RILEY M. BOVE

Clinical Research Protocol

BAZEDOXIFENE ACETATE AS A REMYELINATING THERAPY FOR PATIENTS WITH MULTIPLE SCLEROSIS

Protocol Number:	0003
Version Date:	08/27/2019
Investigational Product:	Bazedoxifene
IND Number:	138495
Development Phase:	Phase II
Sponsor:	Riley Bove, MD 675 Nelson Rising Lane Weill Institute for the Neurosciences San Francisco, CA 94158
Funding Organization:	Sherak Foundation
Principal Investigator:	Name: Riley Bove, MD Telephone: (415) 595-2795 Fax: N/A E-mail: riley.bove@ucsf.edu
Medical Monitor:	Name: Jeffrey Gelfand, MD Telephone: (415) 680-4900 Fax: N/A E-mail: Jeffrey.Gelfand@ucsf.edu

Approval:

Riley M Bove, MD *Assistant Professor of Neurology* — 08.27.2019

PI or Sponsor Signature (Name and Title) — *Date*

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Riley M. Bove with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 0002

Protocol Title: BAZEDOXIFENE ACETATE AS A REMYELINATING THERAPY FOR PATIENTS WITH MULTIPLE SCLEROSIS

Protocol Date: 08/06/2019

Riley M Bove, MD	08.27.2019
Investigator Signature	*Date*

Riley M. Bove, MD, Assistant Professor of Neurology

Print Name and Title

Site # _____

Site Name Weill Institute for the Neurosciences, University of California, San Francisco

Address *675 Nelson Rising Lane*

San Francisco, CA 94158

Phone Number *415.595.2795*

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
BZA	Bazedoxifene acetate
CFR	Code of Federal Regulations
CVLT-II	California Verbal Learning Test-II
eCRF	Electronic Case Report Form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPLC-MS/MS	High-performance Liquid Chromatographic-tandem mass spectrometric method
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
mEq	milliequivalent
MFIS	Modified Fatigue Impact Scale
MfVEP	Multi Focal Visual Evoked Potential
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSWS-12	Multiple Sclerosis Walking Scale
OCT	Optical Coherence Tomography
OPC	Oligodendrocyte progenitor cells
PI	Principal Investigator
RNFL	Retinal Nerve Fiber Layer

RRMS	Relapsing Remitting Multiple Sclerosis
SAE	serious adverse experience
SDMT	Symbol Digit Modality Test
SERM	Selective Estrogen Receptor Modulator
T25W	Timed 25-foot Walk
TUG	Timed-Up-and-Go
VEP	Visual Evoked Potential

PROTOCOL SYNOPSIS

TITLE	Bazedoxifene acetate as a remyelinating therapy for patients with MS
SPONSOR	Dr. Riley M Bove
FUNDING ORGANIZATION	Sherak foundation
NUMBER OF SITES	1
RATIONALE	Multiple Sclerosis (MS) is a chronic neurologic disorder characterized by the loss of myelin, which results in disruption of nerve signal, damage to axons, and, ultimately, neurodegeneration. In order to treat MS, new methods for promoting repair (remyelination) are sorely needed. There is a strong preclinical (including EAE)[7] and epidemiologic rationale for investigating the remyelinating potential of estrogenic compounds, including evidence of endogenous (puberty, postpartum periods)[8] and exogenous hormonal influences on MS risk[9-14] and course.[15,16] MS affects 3 times more women than men, and disease course in women appears overall less aggressive (on MRI, fewer T2-hyperintense demyelinated lesions develop into axonal destruction visualized as hypointense T1 "black holes"[8,17]). BZA, a third-generation SERM with extensive safety data in humans, was identified in a novel high-throughput screen (BIMA screen) for compounds capable of promoting remyelination. Subsequent analysis validated BZA's remyelinating effect *in vitro* and *in vivo* following demyelinating insult. Given strong pre-clinical support for BZA's remyelinating potential, and the clinical success of other compounds identified using the BIMA screen (Green et al., 2017), we propose the investigation of BZA as a remyelinating therapy in MS.
STUDY DESIGN	This is a single-center, double blind, randomized, controlled, delayed-start Phase 2 clinical trial investigating the remyelinating effects of BZA relative to placebo.
PRIMARY OBJECTIVE	The primary objective is to evaluate the efficacy of BZA relative to placebo for reducing P100 latencies on full field transient pattern reversal visual evoked potentials at 90 days in a double-blinded trial (1st 90 days in Group A versus 1st 90 days of Group B.)

SECONDARY OBJECTIVES	● The first key secondary objective is to assess whether latency delay at 180 days decreases to a greater extent in Group A (exposed to BZA for 90 days during both Stage 1 and Stage 2) when compared to Group B (exposed to placebo during Stage 1 and BZA for only 90 days during Stage 2). ● The second key secondary objective is to demonstrate the tolerability of BZA in this population. This will include special focus with regards to fatigue as this is a major symptom for patients suffering from multiple sclerosis. ● The third key secondary objective is to document the safety of BZA in this population of patients. ● The fourth key secondary objective of this study is to help assess which secondary and tertiary outcomes are likely to be informative for future remyelinating trials in multiple sclerosis.
NUMBER OF SUBJECTS	50
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Relapsing remitting Multiple Sclerosis by 2017 Revised McDonald Criteria 2. Women aged 45-65 or 40+ post-menopausal. 3. Latency delay > 118 milliseconds on baseline full-field transient pattern reversal VEP in at least one eye (electrophysiological evidence of demyelination) 4. RNFL > 70 microns on SD-OCT in the same eye meeting criteria for latency delay (sufficient axons) 5. Stable immunomodulatory therapy – no switch or planned switch in > 6 months and no change in doses in 30 days prior to screening 6. Use of contraceptive method with ≤1% failure rate during period of trial if premenopausal 7. Understand and sign informed consent. 8. EDSS 0-6.0 (inclusive) Exclusion Criteria: 1. Multiple Sclerosis disease duration > 25 years 2. Optic neuritis in prior 6 months 3. Known optic neuritis in involved eye ≥ 10 years ago 4. Major ophthalmologic disease/Concomitant ophthalmologic disorders (e.g. diabetes, macular degeneration, glaucoma, severe myopia, etc.). 5. Myopia > -7 Diopters (severe myopia) 6. Disc hemorrhages in qualifying eye 7. No light perception in qualifying eye 8. Simultaneous bilateral optic neuritis

	9. Cotton wool spots in qualifying eye 10. Macular star in qualifying eye 11. History of significant cardiac conduction block 12. History of cancer (except non-melanoma skin cancer) 13. Suicidal ideation or behavior in 6 months prior to baseline 14. Pregnancy, breastfeeding, or planning to become pregnant 15. Included with other study protocol simultaneously without prior approval 16. Concomitant or prior use of any other putative remyelinating therapy as determined by investigator, including but not limited to Clemastine, Duavee, and Tamoxifen. 17. Serum creatinine > 1.5mg/dL; AST, ALT, or alkaline phosphatase > 2 times the upper limit of normal 18. History of drug or alcohol abuse within the past year 19. Untreated B12 deficiency (as determined by B12 serological assessments and metabolites including methylmalonic acid [MMA] and homocysteine) or untreated hypothyroidism 20. Clinically significant cardiac, metabolic, hematologic, hepatic, immunologic, urologic, endocrinologic, neurologic, pulmonary, psychiatric, dermatologic, allergic, renal or other major diseases that in the PI's judgement may affect interpretation of study results or patient safety. 21. History of or presence of clinically significant medical illness or laboratory abnormality that, in the opinion of the investigator would preclude participation in the study. 22. Patients whose lack of mobility exposes them to an increased risk of venous thromboembolism 23. Patients with undiagnosed uterine bleeding 24. Patients with unknown, suspected or past history of breast cancer 25. Patients with known or suspected estrogen-dependent neoplasia 26. Patients with active or a past history of venous thromboembolism 27. Patients with active or a past history of arterial thromboembolism 28. Patients with known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders 29. Patients with hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any ingredients 30. Patients with known hepatic impairment or disease
TEST PRODUCT, DOSE, AND ROUTE	40mg of bazedoxifene acetate (Conbriza) Product will be taken daily via oral administration of 2 20mg Conbriza

OF ADMINISTRATION	tablets for the duration of treatment period (180 days for 'Early-start' group and 90 days for 'Delayed-start' group). Tablets will be over-encapsulated in gelatin capsules for proper blinding.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Microcrystalline cellulose placebo Product will be taken daily via oral administration of 2 tablets for duration of the treatment period (first 90 days of 'Delayed-start' group ONLY). Tablets will be over-encapsulated in gelatin capsules for proper blinding.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 200 days ***Screening:*** *2 weeks* ***Treatment:*** *6 months* *The total duration of the study is expected to be 24 months, which includes 18 months for subject recruitment.*
CONCOMMITANT MEDICATIONS	Allowed: MS disease modifying and symptomatic therapies, antidepressants (no adjustments within 2 months of baseline visit) Prohibited: hormone therapies (estrogen, testosterone, progesterone), hot flash therapies; lamotrigine, oxcarbazepine
EFFICACY EVALUATIONS	This study includes the following efficacy assessments: • Detailed neurological examination, including the determination of EDSS score, will take place at the baseline and 6-month visits. • Magnetic Resonance Imaging (MRI) scans will be performed at the baseline, 3-month, & 6-month visits. • High and Low Contrast Visual Acuity (2.5% ETDRS) will be assessed at every visit. • Optical Coherence Tomography (OCT) will be performed at screening, baseline, and 6-month visits. • Full-field Visual Evoked Potential will be performed at every visit. • Cone contrast testing will be performed at baseline and 6 month visits. Note: Prior to each visit, participants should be reminded to bring with them any corrective lenses that they use on a regular basis for reading, distance, or both. If the participant does not have or if they forget their corrective lenses, a pair of trial lenses will be provided during the visit.
PRIMARY ENDPOINT	Remyelination assessed by the reduction of P100 VEP latency
SECONDARY ENDPOINTS	[Imaging]: Whole brain MTR, white matter MTR, white matter fractional anisotropy (FA), and MWF. [Functional]: Low-contrast letter acuity (LCLA)
OTHER EVALUATIONS	

SAFETY EVALUATIONS	Phone call at week 6 to see if patient is experiencing any unacceptable side effects. When approximately 50% of patients have completed the study through Study Visit 2 (total visit 3), an interim analysis for safety will be conducted by the PI. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study. Incidence of adverse events.
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through Study Visit 2 (total visit 3), an interim analysis for safety will be conducted by the PI. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	Data will be analyzed per protocol utilizing an intention to treat approach including all patients randomized to the study for the principal analysis. Loss to follow up will be accounted for using standard statistical methods. The principal analysis will be performed using mixed effects linear regression model controlling for clustering by eye.
Rationale for Number of Subjects	With 25 patients per group the study has 90% power to detect a 50% relative reduction in latency with BZA compared to placebo at the 3-month outcome for group 1 assuming a two-sided test with alpha = 0.05. Study size may be expanded to compensate for dropouts over the short study period. To maximize study efficiency and resource utilization these subjects will not be enrolled unless necessary.

1 BACKGROUND

Here, we propose a Phase II DBRCT, delayed start protocol, to evaluate the effect of bazedoxifene 40mg vs. placebo on promoting remyelination in women with multiple sclerosis (MS), as measured by Visual Evoked Potentials.

Multiple sclerosis (MS) is the most prevalent chronic, non-traumatic neurological disorder among young adults; MS affects approximately 400,000 people in the United States and 2.1 million people around the world[1]. There is no single diagnostic test for MS; diagnoses are made on the recognition of clinical disease patterns and the exclusion of alternatives.[2] [3] Most notably, patients are required to exhibit the spatiotemporal dissemination of lesions, meaning that evidence of prior demyelinating injury must be present at the time of diagnosis. The myelin sheath is an integral accessory to functioning nerve fibers and provides multiple layers of concentric membrane to axons, which serves to increase conduction velocity and reduce energetic cost of action potentials.[4] Myelin loss in MS results in disruption of the nerve signal, axonal damage, and ultimately neurodegeneration. To effectively prevent the downstream effects of myelin injury, novel approaches to promote repair will be required.

There is a strong preclinical (including EAE)[7] and epidemiologic rationale for investigating the remyelinating potential of estrogenic compounds, including evidence of endogenous (puberty, postpartum periods)[8] and exogenous hormonal influences on MS risk[9-14] and course.[15,16] MS affects 3 times more women than men, and disease course in women appears overall less aggressive (on MRI, fewer T2-hyperintense demyelinated lesions develop into axonal destruction visualized as hypointense T1 "black holes"[8,17]). PI Dr. Bove has shown that the 10% of MS women with post-menopausal onset of symptoms do not appear to be "protected" from progression typical of their male counterparts.[18] Further, she has shown that MS disease severity may worsen with ovarian aging.[19,20] This age-related decline in gonadal steroids might represent a *sex-specific* influence[21] on age-related disability progression,[22] and on decreased CNS resilience—including through remyelination—in the face of neuroinflammatory injury.

Selective Estrogen Receptor Modulators (SERMs) provide more tissue-selective, full or partial agonism or antagonism of estrogen receptors (ERα and ERβ).[25] It is widely believed that modulation of ERα and/or ERβ induces neuroprotection through remyelination.[26] Supportive observations include the classic SERM tamoxifen leading to decreased severity of EAE symptoms and of demyelination,[27] and that the potent, selective ERβ agonist indazole-chloride (Ind-Cl) induces corpus callosum remyelination in the cuprizone-induced demyelination mouse model of MS.[28] However, the SERM compounds currently examined, such as tamoxifen, have significant tolerability limitations (e.g. hot flashes), which limit their clinical application.[29] In contrast, multiple other agents within this class have demonstrated pharmaceutical indications (osteoporosis, cancer prevention) and are more tolerable. Bazedoxifene (BZA) is a SERM recently FDA-approved in combination with conjugated estrogens (CEs) as Duavee. BZA offsets estrogenic stimulation of endometrial and breast tissue, and CE 0.45mg/BZA 20mg is approved for menopausal hot flash relief and osteoporosis prevention, with a favorable tolerability and safety profile.[25,30] In the brain, limited data suggest that BZA may

counteract inflammation under neurodegenerative conditions by targeting the production and release of pro-inflammatory molecules by glial cells.[31-33] In a male rat model of transient focal cerebral ischemia, BZA exerted neuroprotective actions mainly in the cortical region, and estradiol at the subcortical level.[34] Further, our pre-published work presented at this year's joint Americas—European Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS—ECTRIMS) conference in Paris, demonstrates that BZA enhances OPC differentiation *in vitro* and *in vivo* and promotes functional remyelination (Bove et al., ECTRIMS 2017).

To date, the clinical remyelinating effects of BZA are unknown.

1.1 Overview of Non-Clinical Studies

Screening for small molecules or biologicals that promote remyelination represents a promising avenue for the identification and development of reparative treatments for MS,[23] but a significant hurdle for the rational advancement of compounds identified in screens remains the functional confirmation of myelin repair. Recent technical advances with screening platforms provide us with this unique opportunity to provide insight into the cell autonomous mechanisms for remyelination and address this unmet need in MS.

SERMs have been identified as compounds capable of promoting oligodendrocyte differentiation using several recent unbiased screens for remyelination,[24] including BIMA (**B**inary **I**ndicant for myelination using **M**icropillar **A**rrays), a functional high-throughput screen developed by the Chan Laboratory at UCSF.[1] BIMA involves freestanding micropillar arrays of compressed silica around which myelin rings of membrane wrapping by oligodendroglia can be visualized in cross-section. These micropillars are placed in 96- and 384-well formats, testing therapeutic compounds' direct influences on oligodendroglia without indirect effects from neurons.

Using this high throughput screen, BZA, was identified as a bioactive compound with strong remyelinating potential (platform presentation, AAN 2017 Annual Meeting). Our pre-published work validated this finding *in vitro* and *in vivo*; OPCs were derived from WT P7 rat pups using previously validated methodology (Mei et al., 2014), cultured in isolation, and treated with increasing concentrations (5-500nM) of BZA for 48 hours. At all concentrations (5nM to 500nM) BZA significantly enhanced OPC differentiation and subsequent myelination (platform presentation, AAN 2017 Annual Meeting [44]). Following a lysolecithin induced toxic, focal demyelinating injury to the corpus collosum of 8-week old adult mice, daily BZA delivered via oral gavage resulted in enhanced differentiation and an increased number of oligodendrocytes in the lesion area when compared to controls. Given subsequent *in vitro* analysis of BZA's differentiation effect on OPCs isolated from ERα and ERβ null mice (not shown), which revealed a remyelinating mechanism that is independent of either ER, we performed the same *in vivo* analysis on ERα-ERβ double knockout mice. Comparable OPC differentiation and remyelination following focal demyelination confirmed that the potent reparative effects of BZA is maintained in the absence of ERs.

1.2 Overview of Clinical Studies

Remyelination. Recently published work from the collaborating Chan and Green Labs at UCSF, provides strong support for the BIMA screening method's ability to identify remyelinating compounds with strong translational potential. Clemastine, a first-generation antihistamine, which is known to readily cross the blood-brain-barrier and has been available as an 'over the counter' in the U.S. since 1992, was identified using this screen and subsequently tested in a clinical trial

assessing it's remyelinating potential in patients with MS. This trial (NCT02040298) used VEP latency, a well-validated measure of remyelination, to gauge Clemastine's therapeutic efficacy over the course of the trial period. To date, this remains the only randomized controlled trial to document efficacy of a remyelinating drug for chronic demyelinating injury in MS (Green et al., 2017). These findings support the investigation of compounds with high translational potential that have been identified in BIMA screens.

Bazedoxifene in clinical trials. The recent FDA approval of Duavee (BZA + conjugated estrogens) in the U.S was largely dependent on safety and efficacy data obtained from the Selective estrogens, Menopause, And Response to Therapy (SMART) trials. The first SMART trial, SMART-1, included 3,397 subjects who took at least one dose of the study drug; of this group, 840 participants received the same daily dose of BZA (40 mg) as is outlined in this protocol. At the end of the 2-year study, the incidence of adverse events did not differ significantly when compared to placebo, nor were significant differences observed between the 20 mg and 40 mg BZA groups (Pickar et al., 2009). Subsequent SMART trials underscore the safety of BZA in humans but do not include 40 mg treatment groups, as 20 mg was determined to be the lowest effective dose.

The approval of Conbriza (BZA) in the E.U. and Viviant (BZA) in Asia are also supported by several large-scale Phase I-III clinical trials documenting safety and efficacy. In a 3-year, randomized, placebo-, and active-controlled clinical trial assessing the efficacy of BZA in reducing vertebral fracture risk in postmenopausal women with osteoporosis, more than 3,750 women took daily BZA, 1,872 of them at a daily dose of 40 mg. BZA was well tolerated across all treatment doses over the 3-year period of therapy and was shown to be effective in reducing risk of vertebral fracture, increasing BMD of the hip and spine, and reducing bone turnover (Silverman et al., 2008). Multiple other studies, albeit slightly smaller in scale, include treatment groups where patients received daily 40 mg BZA (Itabashi et al., 2011; Miller et al., 2008; Ronkin et al., 2005) and exhibit a favorable safety and tolerability profile.

2 STUDY RATIONALE

BZA is an approved medication in the EU and Japan (Conbriza and Vivant, respectively) for the treatment of postmenopausal osteoporosis in women at increased risk of fracture. Multiple longitudinal, multicenter Phase I-III trials have unequivocally supported the use of BZA in human populations matching our inclusion criteria for age and sex (Itabashi et al., 2011; Miller et al., 2008; Pickar et al., 2009; Ronkin et al., 2005; Silverman et al., 2008). We are confident in these safety data, which underscore the minimal assumption of risk, and believe the benefit to individual patients with MS—and the scientific community as a whole—to be far greater than the burden of reasonably occurring treatment emergent adverse reactions.

2.1 Risk / Benefit Assessment

The potential benefit resulting from participation in this study is immense—both for the individual and the scientific community. If our preclinical findings, indicating BZA's therapeutic potential for remyelination, are upheld in patients with MS, it will represent a significant step towards fulfilling the long unmet need for reparative treatments. These potential benefits outweigh the minimal risk assumed in participation in this study.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the efficacy of BZA relative to placebo for reducing P100 latencies on full field transient pattern reversal visual evoked potentials at 90 days in a double-blinded trial (1st 90 days in Group A versus 1st 90 days of Group B.)

3.2 Secondary Objectives

- The first key secondary objective is to assess whether latency delay at 180 days decreases to a greater extent in Group A (exposed to BZA for 90 days during both Stage 1 and Stage 2) when compared to Group B (exposed to placebo during Stage 1 and BZA for only 90 days during Stage 2).
- The second key secondary objective is to demonstrate the tolerability of BZA in this population. This will include special focus with regards to fatigue as this is a major symptom for patients suffering from multiple sclerosis.
- The third key secondary objective is to document the safety of BZA in this population of patients.
- The fourth key secondary objective of this study is to help assess which secondary and tertiary outcomes are likely to be informative for future remyelinating trials in multiple sclerosis.

Additional Secondary Objectives:

- To evaluate the efficacy of BZA relative to placebo in increasing magnetization transfer ratios derived from magnetic resonance imaging of the brain during the period of exposure to active treatment.
- To evaluate the efficacy of BZA relative to placebo in reducing latency delay on multifocal visual evoked potentials during the period of exposure to active medication.
- To evaluate the efficacy of BZA relative to placebo at reducing radial diffusivity derived from diffusion tensor imaging as assessed by magnetic resonance imaging during the period of exposure to active medication.
- To evaluate the efficacy of BZA in reducing the EDSS score at the end of Stage 1 (Group A exposed to BZA for 90 days, Group B exposed to placebo for 90 days), as well the efficacy of BZA in reducing EDSS at the end of Stage 2 (after 180 days of BZA in Group A and 90 days of placebo + 90 days of BZA in Group B).
- To evaluate the efficacy of BZA relative to placebo in improving Symbol Digit Modalities Test (SDMT) performance at the end of Stage 1 and at the end of Stage 2.

4 STUDY DESIGN

4.1 Study Overview

This is a 6-month randomized, single center, double blinded, delayed start study in 50 patients with relapsing remitting multiple sclerosis and identified injury to the anterior visual pathway.

Patients will be randomized 1:1 into two groups: Group A and Group B. Group A will receive 180 days of Bazedoxifene while Group B will receive 90 days of placebo followed by 90 days of Bazedoxifene. Patients will receive two fixed oral tablets of 20mg Bazedoxifene (Conbriza) daily (to be taken at the same time). Patients will be permitted to remain on their standard disease modifying treatment during the course of the study.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Visual evoked potentials (VEPs) are cortically generated electrical potentials recorded over the scalp in response to a visual stimulus. After stimulation, a transient, cortically generated response is tied to the relevant stimulus (the transient VEP) and consists of a series of potentials that are alternately positive and negative in polarity. They are labeled on the basis of their polarity and latency. In most individuals, the first response of the full- field pattern-reversal VEP recorded mid-occipitally is a negative deflection termed the N75. However, given lack of consistency of both the presence and latency of the N75, by convention full-field VEPs usually are assessed by evaluating the first major positive deflection that occurs in normal individuals at around 100 msec and is therefore designated the P100 component. Latency of the VEP is defined as the time from the stimulus to a pre-specified feature of the record.

Following application of scalp leads by the technician, patients will be seated in front of a CRT screen. VEPs will be performed using a single Nicolet VEP instrument under standardized conditions of luminance, distance and check contrast. Check size will be held at 32 minutes of arc as calculated by the formula M = 3438*W/D (M = minutes of arc; W = width of an individual check; D = distance from screen in mm). Standard recording time is approximately 25-30 minutes including the time required for application of the leads. The participant will be instructed to wear corrective lenses if they have them. If they do not, they will be provided with a pair of trial lenses. The primary outcome of interest will be the P100 latency although other parameters may be studied at a later date in secondary analyses.

5.2 Secondary Efficacy Endpoints

5.2.1 Expanded Disability Status Scale (EDSS)

EDSS Score will be determined, based on neurological examination, by a trained certified EDSS rater at scheduled visits according to Appendix-1 using the validated Neurostatus scoring system. Whenever possible, individual patients will have EDSS performed by same rater on each visit.

The EDSS is an ordinal scale used for assessing neurological impairment of MS based on a neurological examination. It consists of scores in each of seven functional systems (FS) and an ambulation score that are then combined to determine the EDSS [ranging from 0 (normal) to 10 (death due to MS)]. The FSs are the Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions. The FSs and EDSS steps will be assessed in a standardized

manner. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and longitudinally, to assess disability progression in clinical studies in MS.

Disability progression based on the EDSS is defined as an increase from baseline of 1 point (in patients with a baseline EDSS score of 3.0 to 5.0 inclusive) or of 0.5 point (in patients with a baseline EDSS score of 5.5 to 6.5 inclusive). To confirm that the progression is sustained, this increase should, at a minimum, be present at a visit at least 3 months later (for 3-month confirmed disability progression) with any intervening EDSS values also meeting the criteria for change.

Analysis of disability progression based on the EDSS score will include variables such as:

- Time to 3-month confirmed disability progression
- Proportion of patients free of a 3-month confirmed disability progression

5.2.2 Magnetic Resonance Imaging (MRI)

All patients will undergo MRI scanning of the brain according to the schedule in Appendix-1. MRI evaluation will include, but is not limited to:

Sequences:

- Magnetization Transfer Ratio (5 minutes)
- Radial diffusivity on Diffusion Tensor Imaging (9 minutes)
- T1, FLAIR (10 minutes)
- 3D T2 star (10 minutes)
- Number of new/ enlarging T2 hyperintense lesions
- Total volume of T2 lesions
- Volume of T1 hypointense lesions
- Change in brain volume

All images will be obtained on a Siemens Skyra 3T MRI in the Sandler Neurosciences Building. All scans will be performed by a trained MRI technician using protocols previously defined within the lab (specific MR settings to be defined elsewhere).

Each MRI scan performed for the study, both scheduled and unscheduled (e.g. ordered by the investigator for safety or differential diagnosis), will be reviewed by a neuroradiologist and the primary treating physician must be contacted in case of unexpected findings (not consistent with optic neuritis) detected on the MRI scan for safety actions and Adverse Event reporting.

During the study each scan performed, both scheduled and unscheduled, will be assessed by the blinded trained physician from the NICMSMRI team. Upon acquisition the MRI will be evaluated for quality, completeness, and adherence to the manual. Confirmation of MRI quality or a description of the quality problems, if detected, will be communicated to the investigators. If scan is incomplete or incorrectly performed, the study center will be asked to repeat it as soon as possible. After completion of the quality check, all scans will be analyzed according to a standardized procedure.

Scanning:

All sequences will be performed according to lab specifications.

MRI scans will include MTR, Diffusion tensor imaging, myelin water fraction, T1-weighted images, T2-weighted, Proton Density-weighted and FLAIR images.

5.2.3 Cognition

5.2.3.1 Symbol Digit Modalities Test (SDMT)

The SDMT will be assessed according to the schedule in Appendix-1 (study coordinator to administer). The SDMT is a sensitive and specific test to assess processing speed and working memory which are typically affected domains in cognitively impaired MS patients. During the administration of the SDMT, only the examiner and the patient should be in the testing room. The examiner can be the study coordinator, independent EDSS rater or a qualified individual not involved in the treatment of the patients who has been instructed in the appropriate administration of the test. Patients are presented with a test instrument at the top of which there is a row of nine numbers paired with unique symbols. Below this part of the test instrument is an array of symbols paired with empty spaces, the patient's task is to match the number for each symbol as quickly as possible. The test takes approximately 5 minutes to administer. The test scoring is calculated based on the number of correct answers in 90 seconds.

5.2.3.2 Additional cognitive tests

Each study participant will complete approximately 10-15 minutes of cognitive testing as part of three separate study visits (baseline visit, 3-month visit, 6-month visit). The cognitive measures will be administered by a trained study research assistant at the UCSF Multiple Sclerosis Center. In addition to the SDMT, participants will complete the California Verbal Learning Test-II (CVLT-II), an assessment of verbal learning and memory with robust normative data in both healthy and MS populations. This task involves the immediate recall of a list of 16 nouns read aloud by the evaluator at one-second intervals.

5.2.4 High Contrast / Low Contrast Visual Acuity (LCVA)

Visual acuity will be assessed according to the schedule in Appendix-1. Disturbances in visual function are common in patients with optic neuritis but these impairments are often not readily apparent on commonly used high-contrast acuity tests. The use of low-contrast visual acuity charts has therefore gained validity in the assessment of visual acuity in patients with optic neuritis. Low contrast Sloan letter charts provide a practical, quantitative, and standardized assessment of visual function. Each chart consists of rows of gray letters, decreasing in size from the top to the bottom row, on a white background. A complete set consists of 7 charts, each with a different level of contrast ranging from 100% (normal vision chart) to 0.6%. For this study only two charts will be used, the 100% (normal vision chart) and 2.5% contrast charts.

When these charts are being rated it is important that standardized conditions are used (e.g. distance from the chart, lighting conditions). For high contrast testing, participants will be seated 4 meters from the chart. For low contrast testing, participants will be seated 2 meters from the chart. Letter scores indicate the number of letters identified correctly, each chart is scored separately. In both cases, testing will be conducted in a low-luminance setting.

Low-contrast letter acuity testing with Sloan charts is easy to administer and has been shown to have high inter-rater reliability both in patients with optic neuritis and in healthy volunteers. The participant will be instructed to wear corrective lenses if they have them. If they do not, they will be provided with a pair of trial lenses.

To ensure consistency amongst raters and between sites, a standard prompt will be utilized for test administration. The administrator will ask the participant to begin at the top line of the chart, reading each line completely and down as many lines as possible. When the

participant finishes reading the chart, they will be prompted by the tester one time: "Please give the next line your best attempt." The tester may continue to encourage the participant following the successful (greater than or equal to 4/5 letters correct) completion of each line until the participant can read no further.

5.2.5 Optical Coherence Tomography (OCT)

OCT will be assessed according to the schedule in Appendix-1. Optical Coherence Tomography (OCT) is a noninvasive, noncontact, trans-pupillary imaging technology which can depict retinal structures in vivo with high resolution cross-section images of the retina (axial resolution of 3- 5 microns). Cross-sectional images of the retina are produced using the optical backscattering of light in a fashion analogous to B-scan ultrasonography. Whereas ultrasound produces images from backscattered sound "echoes," OCT uses infrared light waves that reflect off the internal microstructure within the biological tissues. The frequencies and bandwidths of infrared light are orders of magnitude higher than medical ultrasound signals -- resulting in greatly increased image resolution approximately 8-25 times greater than any existing modality. In addition, the anatomic layers within the retina can be differentiated and retinal thickness can be measured.

Infrared light is delivered to the imaging site through a single optical fiber only .006" diameter (about the size of the period in this sentence). The imaging guide wire contains a complete lens assembly to perform a variety of imaging functions. Guide wire can be deployed independently or integrated into existing therapeutic or imaging catheters.

While standard electronic techniques are adequate for processing ultrasonic echoes that travel at the speed of sound, interferometric techniques are required to extract the reflected optical signals from the infrared light used in OCT. The output, measured by an interferometer, is computer processed to produce high-resolution, real time, cross sectional or 3-dimensional images of the tissue. This powerful technology provides in situ images of tissues at near histological resolution without need for excision or processing of the specimen.

Image scanning will be performed on a Heidelberg Spectralis Spectral Domain OCT instrument. Scanning protocols will include peripapillary B scan and 19 B scan Macular raster scan with target ART of 100 and 50 respectively. Quality targets will be 25 for all studies and only studies with Q> 20 will be analyzed.

5.2.6 Health Status Questionnaire (SF-36)

For this study, a Health Status Questionnaire will be administered to patients at the three time-points indicated in Appendix-1. The questionnaire falls under the comprehensive Multiple Sclerosis Quality of Life Inventory (MSQLI), which was developed by The Consortium for Multiple Sclerosis Centers Health Sciences Research Subcommittee as a comprehensive outcomes assessment battery (Fisher et al, 1999), and it will allow us to monitor the participants' quality of life with regard to their health.

The Short Form-36 (SF-36) was derived from the General Health Survey of the Medical Outcomes Study in 1988. As cited by the Multiple Sclerosis Society, it is one of the most widely used generic measures of health-related quality of life and has been shown to discriminate between

subjects with different chronic conditions and between subjects with different severity levels of the same disease. The SF-36 has also demonstrated sensitivity to significant treatment effects in a variety of patient populations.

This tool addresses health issues that are relevant to MS patients from the patient's perspective. The SF-36 generates two summary scores based on 8 subscales. The two scores arrived at are the physical component summary and the mental component summary.

5.2.7 Cone Contrast testing

Rabin cone contrast testing will be performed at the visits indicated in Appendix 1. The test will be performed using an Innova Provideo CCT. Cone sensitivity threshold testing is used to accurately detect shifts the may indicate the onset of eye disease. The participant will be seated so that their eyes are approximately 2 meters from the center of the monitor. They will be instructed to wear corrective lenses if they have them. If they do not, they will be provided with a pair of trial lenses. The participant will be instructed to choose the letter that they see on the screen using a wireless computer mouse. Each eye will be tested individually.

The test presents colors that use only one of your three cones types and shows the color progressively fainter to individually score how the cones are functioning. Using a combination of color and contrast, the Rabin Cone Contrast test is a quantifiable measure of color vision, allowing detection of both hereditary and acquired color vision loss.

Cone contrast testing will be used to assess whether BZA versus placebo has any effect on preservation of color sensitivity.

5.3 Safety Evaluations

5.3.1 Physical Examination

A complete physical examination will be performed by blinded clinician at the visits indicated in Appendix-1 and will include assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function, and comments on general appearance. All significant findings that are present prior to signing informed consent must be reported on the relevant medical history/ current medical conditions eCRF. Significant findings made after signing the informed consent and being randomized meets the definition of an Adverse Event and must be recorded on the Adverse Event case report form through UCSF's clinical database, REDCap.

5.3.2 Vital Signs

Vital signs will include height, sitting pulse rate, sitting systolic and diastolic blood pressure and body temperature which will be assessed at the visits indicated in Appendix-1.

Clinically notified vital signs are defined in Appendix 1.

5.3.3 Height and Weight

Height will be assessed at the screening visit in centimeters/ inches.

Weight will be assessed in kilograms at the visits indicated in Appendix-1.

Body weight in indoor clothing, but without shoes will be measured. Participants should be asked to remove any items from their pockets and remove any outside clothing such as scarves, jackets, gloves, etc.

5.3.4 Ophthalmologic Examination

Patients will undergo screening ophthalmologic exam to include assessment for any undiagnosed ophthalmologic disease that could impact assessments including but not limited to dilated examination of the fundus and macula by study investigator. This evaluation will include an eye history, visual acuity measurements and dilated ophthalmoscopy at the screening visit.

Patients with a history of, or active uveitis or a history of macular edema will require special attention.

In addition to visual acuity assessments and dilated ophthalmoscopy, measurement of retinal thickness by OCT and measurement of VEP latency will be conducted at visits as indicated in Appendix-1. The PI will complete an examination of worksheet which will then be transcribed to an ophthalmologic examination eCRF.

5.3.5 Fatigue Assessment

To ensure patient safety in daily activities, we will conduct a fatigue assessment at each of the visits indicated in Appendix-1, in order to monitor the degree of self-reported fatigue experienced.

The Modified Fatigue Impact Scale (MFIS) is a 21-item fatigue scale that measures the physical, cognitive, and psychosocial aspects of fatigue.

5.3.6 Other Assessments

MS is associated with a variable combination of symptoms, including sensory loss, imbalance, mobility loss, bladder and bowel dysfunction, cognitive dysfunction, spasticity, pain, and sexual dysfunction. Measurements of these wide-ranging effects of MS on the lives of patients is beyond the scope of the clinician-reported endpoints commonly used to evaluate therapeutic effectiveness in MS studies. Patient-reported outcome (PRO) measures provide an empirical assessment from the patient s perspective of the benefits of treatment that cannot be gained from Magnetic Resonance Imaging (MRI), Expanded Disability Status Score (EDSS), or Optical Coherence Tomography (OCT).

5.3.7 Adverse Event Reporting Plan

This study is investigator-sponsored and does not involve any outside sponsoring institution to which adverse events should be reported. Serious Adverse Events (SAEs) or unanticipated adverse events, therefore, will be reported internally to the UC San Francisco Committee on Human Research within 10 working days of the event s occurrence according to requirements outlined in the CHR's reporting guidelines.

All adverse events during this study will be recorded in real time in UCSF's HIPAA approved clinical database, REDCap. Recording such events in the same database each paten's trial-based visit records will allow for more efficient tracking and monitoring of all adverse events within the study.

In addition, an inventory of adverse events will be obtained at each visit.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a clinically definite diagnosis of MS—according to the 2017 revised McDonald Criteria (Thompson et al., 2017)—who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Women aged 45-65 or 40+ post-menopausal.
2. Documentation of a clinically definite diagnosis of relapsing-remitting MS
3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.
4. Latency delay > 118 milliseconds on baseline full-field transient pattern reversal VEP in at least one eye (electrophysiological evidence of demyelination)
5. RNFL > 70 microns on SD-OCT in the same eye meeting criteria for latency delay (sufficient axons)
6. Stable immunomodulatory therapy – no switch or planned switch in > 6 months and no change in doses in 30 days prior to screening
7. Use of contraceptive method with ≤1% failure rate during period of trial if premenopausal
8. Understand and sign informed consent.
9. EDSS 0-6.0 (inclusive)

6.3 Exclusion Criteria

1. Multiple Sclerosis disease duration > 25 years
2. Optic neuritis in prior 6 months
3. Known optic neuritis in involved eye ≥ 10 years ago
4. Major ophthalmologic disease/Concomitant ophthalmologic disorders (e.g. diabetes, macular degeneration, glaucoma, severe myopia, etc.).
5. Myopia > -7 Diopters (severe myopia)
6. Disc hemorrhages in qualifying eye
7. No light perception in qualifying eye
8. Simultaneous bilateral optic neuritis
9. Cotton wool spots in qualifying eye
10. Macular star in qualifying eye
11. History of significant cardiac conduction block
12. History of cancer (except non-melanoma skin cancer)
13. Suicidal ideation or behavior in 6 months prior to baseline
14. Pregnancy, breastfeeding, or planning to become pregnant

15. Included with other study protocol simultaneously without prior approval
16. Concomitant or prior use of any other putative remyelinating therapy as determined by investigator, including but not limited to Clemastine, Duavee, and Tamoxifen.
17. Serum creatinine > 1.5mg/dL; AST, ALT, or alkaline phosphatase > 2 times the upper limit of normal
18. History of drug or alcohol abuse within the past year
19. Untreated B12 deficiency (as determined by B12 serological assessments and metabolites including methylmalonic acid [MMA] and homocysteine) or untreated hypothyroidism
20. Clinically significant cardiac, metabolic, hematologic, hepatic, immunologic, urologic, endocrinologic, neurologic, pulmonary, psychiatric, dermatologic, allergic, renal or other major diseases that in the PI's judgement may affect interpretation of study results or patient safety.
21. History of or presence of clinically significant medical illness or laboratory abnormality that, in the opinion of the investigator would preclude participation in the study.
22. Patients whose lack of mobility exposes them to an increased risk of venous thromboembolism
23. Patients with undiagnosed uterine bleeding
24. Patients with unknown, suspected or past history of breast cancer
25. Patients with known or suspected estrogen-dependent neoplasia
26. Patients with active or a past history of venous thromboembolism
27. Patients with active or a past history of arterial thromboembolism
28. Patients with known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders
29. Patients with hypersensitivity (angioedema, anaphylaxis) to estrogens, bazedoxifene, or any ingredients
30. Patients with known hepatic impairment or disease

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for MS is allowed except for treatments noted in the exclusion criteria described above.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Up to 50 eligible patients will be randomly assigned to 'Early' or 'Delayed Start' treatment groups in a 1:1 ratio using a SAS-based computer-generated randomization scheme developed by the study data management provider. The CTSI statistician advising the PI will complete a randomization worksheet.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled.
- The CTSI statistician advising the PI will perform the randomization/blinding chart and provide this to the Compounding Pharmacy. They will perform interim safety analysis without unblinding the study, and will only unblind the study to the investigators at the end of study.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.
- Packaging and labeling will be done by pharmacy personnel who are not involved in analysis of study data.

The study blind will be broken on completion of the clinical study and after the study database has been locked. The investigators will be given the randomization worksheet from the CTSI statistician after the last participant has completed their study.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with Dr. Riley Bove prior to unblinding.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

BZA is a third-generation selective estrogen receptor modulator (SERM). It is an immediate release, film-coated capsule shaped tablet. Tablets contain 20 mg of bazedoxifene expressed as free base. The tablets are supplied from Pfizer in blister packaging (commercially available Conbriza) and delivered to the compounding pharmacy unopened.

For blinding, it will encapsulated in a gelatin capsule and fill remaining space with microcrystalline cellulose, by Koshland Compounding Pharmacy (Dr. Peter Koshland) at:

Koshland Pharm

301 Folsom Street, Suite B

San Francisco, CA, 94105

(p) 415.344.0600

(f) 415.344.0607

Table 1: Formulation and Measured pH of BZA and Placebo

	2x (BZA, 20 mg)	**Placebo**
Active Ingredient, mg/mL	Bazedoxifene acetate	
Other ingredient, mg/mL	Lactose, microcrystalline cellulose, pre-gelatinised starch	Microcrystalline cellulose

	(maize), sodium starch glycolate, sodium lauryl sulfate, colloidal anhydrous silica, magnesium stearate, ascorbic acid, hypromellose, titanium dioxide (E171) and macrogol 400.	

8.3.2 Formulation of Control Product

Placebo is: Microcrystalline cellulose, encapsulated into a gelatin capsule, taken daily.

8.3.3 Packaging and Labeling

Both the drug and the placebo will be single use daily capsules (2/day) packaged into monthly bottles. Each carton (kit) of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the sponsors, and directions for patient use and storage.

8.4 Supply of Study Drug at the Site

The Sponsor (Dr. Riley Bove) will ship Study Drug to the investigational pharmacy. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made as needed, per pace of enrollment and drug expiration requirements.

The randomization and blinding chart will be provided by CTSI statistician to the pharmacy personnel. Koshland Compounding Pharmacy will then ship the study drug to the PI, and the research team (PI or research coordinator) will give the package to participants at research visits (quantity of study drug determined by expiry of investigational product batch).

8.4.1 Dosage/Dosage Regimen

The medication (BZA or placebo) will be taken once daily, in the morning, for the duration of the study (stage 1 = 3 months, stage 2 = 3 months).

8.4.2 Dispensing

The Koshland Compounding pharmacy will ship the drugs to study personnel, who will then give the samples to the study participants at each research visit. Should the available batch of study drug carry an expiration fewer than 3 months from the time of dispensing, study staff may provide a 1-2month supply at the time of the visit and then re-supply with newer stock via mail or in-person delivery.

8.4.3 Administration Instructions

Patients will take 2 capsules orally once a day.

8.5 Supply of Study Drug at the Site

Study personnel will receive the Study Drug/placebo shipment from the Koshland Compounding Pharmacy and maintain it under locked conditions in the Sandler Neurosciences Center. Subjects will be randomized and provided the study drug on the same day.

8.5.1 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). Subjects will be instructed to store the medication in bottles at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study visits, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at the Screening Visit. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at all Study Visits.

9.1.6 Other Clinical Procedures

Timed Walking Assessments:

T25W: The Timed 25-foot Walk will be assessed according to the schedule in Appendix-1. The Timed Walk is an objective quantitative test of neurological function, and is one of three components of the Multiple Sclerosis Functional Composite (MSFC), a composite measure assessing upper extremity function, ambulation and cognitive function (Fisher et al. 1999). The Timed Walk is an ambulation measurement: a walk of 25 feet (7.62 meters): time taken in seconds. The Timed Walk test will be administered either by the Independent EDSS Rater or by another qualified individual not involved in the treatment of the patients.

6-minute walking distance: The distance subjects can walk in 6 minutes will be assessed on 3 separate occasions as indicated in Appendix-1. The evaluating physician will use a measured hallway to assess the distance subject can walk at safe comfortable speed over a 6-minute period.

Timed up and go (TUG): The TUG test is a valuable measure of subject's gait and postural stability which will be administered according to the schedule in Appendix-1. The test requires that subjects start seated in an arm chair, stand up, walk 3 meters to a designated line, then return to their starting seated position. As a safety precaution, the trained evaluator should maintain a close distance to the subject throughout the test.

Symbol Digit Modalities Test (SDMT):

The SDMT will be assessed according to the schedule in Appendix-1 (study coordinator to administer). The SDMT is a sensitive and specific test to assess processing speed and working memory which are typically affected domains in cognitively impaired MS patients. During the administration of the SDMT, only the examiner and the patient should be in the testing room. The examiner can be the study coordinator, independent EDSS Rater or a qualified individual not involved in the treatment of the patients who has been instructed in the appropriate administration of the test. Patients are presented with a test instrument at the top of which there is a row of nine numbers paired with unique symbols. Below this part of the test instrument is an array of symbols paired with empty spaces, the patient's task is to verbally match the number for each symbol as quickly as possible. The test takes approximately 5 minutes to administer. The test scoring is calculated based on the number of correct answers in 90 seconds.

Low Contrast Visual Acuity (LCVA):

The LCVA will be assessed according to the schedule in Appendix-1. Disturbances in visual function are common in patients with MS but these impairments are often not readily apparent on commonly used high- contrast acuity tests. The use of low-contrast visual acuity charts have therefore gained validity in the assessment of visual acuity in patients with MS. Low contrast Sloan letter charts provide a practical, quantitative, and standardized assessment of visual function. Each chart consists of rows of gray letters, decreasing in size from the top to the bottom row, on a white background. A complete set consists of 7 charts, each with a different level of contrast ranging from 100% (normal vision chart) to 0.6%. For this study only two charts will be used, the 100% (normal vision chart) and 2.5% contrast charts. When these charts are being rated it is important that standardized conditions are used (e.g. distance from the chart, lighting conditions). Letter scores indicate the number of letters identified correctly, each chart is scored

separately. Low-contrast letter acuity testing with Sloan charts is easy to administer and has been shown to have high inter-rater reliability both in patients with MS and in healthy volunteers.

Magnetic Resonance Imaging (MRI)

A baseline MRI scan of the central nervous system (CNS) will be obtained. Both T1 and T2-weighted images will be obtained.

The following parameters will be assessed using these MRI data:

- Myelin water fraction
- Magnetization Transfer Ratio
- Radial diffusivity on Diffusion Tensor Imaging
- Number of new/enlarging T2 hyperintense lesions
- Total volume of T2 lesions,
- Volume of un-enhancing T1 hypointense lesions,
- Change in brain volume

All images will be obtained on the NIC MS Scanner in the Sandler Neurosciences Building. All scans will be performed by a trained MRI technician using protocols previously defined within the lab (specific MR settings to be defined elsewhere). Each MRI scan performed for the study, both scheduled and unscheduled (e.g. ordered by the investigator for safety or differential diagnosis), will be reviewed by a neuroradiologist. The Primary Treating Physician must be contacted in case of unexpected findings (not consistent with MS) detected on the MRI scan for safety actions and Adverse Event reporting. During the study each scan performed, both scheduled and unscheduled, will be assessed by the blinded trained physician from the NIC MS MRI team. Upon acquisition the MRI will be evaluated for quality, completeness, and adherence to the manual. Confirmation of MRI quality or a description of the quality problems, if detected, will be communicated to the investigators. If scan is incomplete or incorrectly performed, the study center will be asked to repeat it as soon as possible. After completion of the quality check, all scans will be analyzed according to a standardized procedure.

For the MRI exam, each participant will be asked a number of questions concerning his or health, lack of metal implants and absence of claustrophobia. They will be asked to lie down on a narrow bed that will then be moved into a tunnel that is 6 feet by 2.5 feet. Each person will need to lie there quietly for about 1.5 hours during which time machine-like banging noises will occur. Earplugs will be provided to reduce the sound level. Communication with the technologists outside will be possible at all times by a microphone and loudspeaker. If the participant wishes to be removed from the magnet, this will be done immediately.

Visual Assessments

A routine functional visual assessment will be made. The investigator will examine the volunteer's eyes (visual acuity, pupil exam, color, motility, King Devick's test for saccades, dilating exam, intraoccular pressure). The patient may be asked to fill out a questionnaire regarding their visual function. Then an OCT will be performed. Ocular Coherence Tomography (OCT) is a special test that evaluates and counts the retinal fiber layer by having the participant focus on a target.

The entire examination will last approximately one hour and 15 minutes (seventy-five minutes) -- some patients will additionally be offered special tests that include:

1. Full-Field visual evoked potential (ffVEP) and multifocal electroretinogram (ERG) are special tests that provide information about optic nerve function by having the participant focus on a constantly changing array of checkerboard lights.

2. Octopus 900 visual field analyzer using a Humphrey's protocol (HVF FDT) or Heidelberg Perimetery (HEP) visual field analyzer are special automated visual field tests that specifically evaluate ganglion cell function by having the participant push a button when they see a light.

This additional testing will require approximately two hours (one-hundred and twenty minutes).

Ophthalmologic Examination

Patients will undergo screening ophthalmologic exam to include assessment for any undiagnosed ophthalmologic disease that could impact assessments including but not limited to dilated examination of the fundus and macula by study investigator. This evaluation will include an eye history, visual acuity measurements and dilated ophthalmoscopy at the screening visit.

Pharmacokinetics/Lab Tests

Participant's serum and PBMCs will be properly stored for later analysis (if needed).

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood will be obtained and sent to each site's clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count), and serum C-reactive protein (CRP) determinations for assessment of systemic evidence for infection and/or inflammation.

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to each site's clinical chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Week 0) - Screening

1. Review the study with the subject and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.

3. Record demographics data.
4. Record medical history, including a history of MS, diagnosis date, and prior MS treatments, as well as history of optic neuritis.
5. Record concomitant medications.
6. Perform a complete physical examination.
7. Perform VEP and OCT assessments (if no record of assessment within past 6 months)
8. Perform and record vital signs.
9. Perform and record results of blood pressure testing.
10. Collect blood for clinical laboratory tests (chemistry, hematology, pregnancy test)
11. Initiate subject diary
12. Schedule subject for Visit 2 in 14 days +/-2.

10.2 Visit 2 (Baseline)

1. Concomitant medications review.
2. Perform abbreviated physical examination.
3. Assess likely side effects via clinician observation and questionnaires
4. Perform and record vital signs.
5. Perform neurologic & ophthalmologic exam.
6. Perform and record visual assessments (OCT, high/low contrast vision testing, cone contrast, VFQ)
7. Perform and record cognitive & other tests (SDMT, MFIS, EDSS, SF-36)
8. Perform timed walking tests (T25W, TUG, 6min walking test)
9. Perform MRI (no contrast)
10. Randomize subject, dispense study drug
11. Collect blood for research laboratory tests (if needed)

10.3 Visit 3 (3-month)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Assess likely side effects via clinician observation and questionnaires
5. Perform and record vital signs.
6. Collect blood for research laboratory tests (if needed)
7. Perform neurologic and ophthalmologic exam.
8. Perform and record visual assessments (high/low contrast vision testing, cone contrast, VFQ)

9. Perform and record cognitive & other tests (SDMT, MFIS, EDSS, SF-36)
10. Perform timed walking tests (T25W, TUG, 6 min walking test)
11. Perform MRI (no contrast)

10.4 Visit 4 (6-month)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Assess likely side effects via clinician observation and questionnaires
5. Perform and record vital signs.
6. Collect blood for research laboratory tests (if needed)
7. Perform neurologic and ophthalmologic exam
8. Perform and record visual assessments (OCT, high/low contrast vision testing, cone contrast, VFQ)
9. Perform and record cognitive & other tests (SDMT, MFIS, EDSS, SF-36)
10. Perform timed walking tests (T25W, TUG, 6 min walking test)
11. Perform MRI (no contrast)
12. Collect blood for clinical laboratory tests (chemistry, hematology)

10.5 Early Withdrawal Visit

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform and record vital signs.
5. Collect blood for clinical laboratory tests (chemistry, hematology)

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature,

severity, or frequency in the current Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines and those outlined in 21CFR312.32. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

This study is investigator-sponsored and does not involve any outside sponsoring institution to which adverse events should be reported. Serious Adverse Events (SAEs) or unanticipated adverse events, therefore, will be reported to the FDA CDER (Center of Drug Evaluation and Research), as well as internally to the UC San Francisco Committee on Human Research (CHR), within respective reporting guidelines.

Unexpected fatal or life-threatening suspected adverse reactions will be reported to the CDER no later than 7 calendar days after initial receipt of the information. UCSF CHR will be notified within 10 working days of the event's occurrence.

Per 21 CFM 312.32(c)(1), any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction will be reported to the CDER no later than 15 calendar days after determining that the information qualifies for reporting.

All adverse events during this study will be recorded in real time in UCSF's HIPAA approved clinical database, REDCap. Recording such events in the same database as each patient's trial-based visit records will allow for more efficient tracking and monitoring of all adverse events within the study.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC as described above.

11.3 Medical Monitoring

Dr. Jeffrey Gelfand should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone : (415) 680-4900
Pager : (415) 443-0871

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 4) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after Visit 3 but prior to Visit 4 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.3 Replacement of Subjects

We plan to enroll 60 participants to consent 50.

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

Safety Data Monitoring throughout the trial: Since this trial is a single-site trial and the overseeing Principle Investigator will be present throughout the trial, a Data and Safety Monitoring Board is not deemed necessary. The study investigator will be responsible for monitoring safety data and adverse events recorded in the patient file and will be responsible for reporting such events to the FDA and IRB.
Safety assessments will be throughout patient visits to ensure patient welfare and safety in daily activities.
Such assessments will include:

- Physical Examination
- Vital Signs
- Height and Weight measurements
- Pregnancy and Assessments of Fertility
- Ophthalmologic Examination

- Fatigue Assessment - Health Status Questionnaire & MFIS
- Pharmacokinetics/Blood tests to assess potential abnormal increase of liver enzymes and serum triglycerides
- Lab tests to assess level of BZA in patient plasma to ensure that they are not abnormal

The Investigator will meet with the study staff biweekly to review safety as well as efficacy data collected from patient visits and assess the safety of the visits and study outcomes.

Patient withdrawal from the study / Stopping rules:
Study treatment must be discontinued for any patient if the investigator determines that continuing would result in a significant risk for that patient. The following conditions/events may be considered sufficient to support a decision about the study drug discontinuation in individual cases:

- Adverse event/serious adverse event
- Abnormal laboratory value(s) or abnormal test result(s)
- Withdrawal of informed consent
- Pregnancy
- Use of prohibited other investigational medications
- Deviations from the prescribed dose regimen for the study drug
- Any other protocol deviation that results in a significant risk to the patient's safety

Discontinuation of the study drug must be recorded along with the patient information in REDCap, giving the date and primary and secondary reasons for stopping study treatment.
The investigator must also contact the Institutional Review Board at the study site (University of California at San Francisco Multiple Sclerosis Center) to register the patient's discontinuation of randomized study drug.
Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.
For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.
If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information with the patient's research data in REDCap as well as report this withdrawal to the Institutional Review Board and FDA CDER, if deemed necessary by the committee.
Patients will be considered to have completed the study if they attend all protocol specified visits and complete all assessments. A patient who discontinues the study medication for any reason, including an adverse event must complete a Safety Follow-Up visit. Any patient still in screening at the time 50 patients have been enrolled will be allowed to continue screening to determine if they will be eligible to enter the study, provided all screening assessments are complete and the randomization visit can occur on or before the designated end of subject recruitment date. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care.
The study can be terminated at any time for any reason by the investigator. Should this be necessary, each patient should be seen as soon as possible and treated as described for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Committee on Human Research of

the trial's early termination.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by dose level: race, gender, age, height and weight.

15.3 Analysis of Primary Endpoint

Data will be analyzed per protocol utilizing an intention to treat approach including all patients randomized to the study for the principal analysis. Loss to follow up will be accounted for using standard statistical methods. The principal analysis will be performed using mixed effects linear regression model controlling for clustering by eye.

15.4 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed using the same methods as primary endpoints.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

15.5 Interim Analysis

After each patient completes the Week 6 phone call, the side effects reported will be analyzed.

When 50% of patients have completed the study through Study Visit 2 (total visit 3), an interim analysis for safety will be conducted by the PI.

Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

15.6 Sample Size and Randomization

With 25 patients per group, the study has 90% power to detect a 50% relative reduction in latency with BZA compared to placebo at the 3-month outcome for group 1 assuming a two-sided test with alpha = 0.05. Study size may be expanded to compensate for dropouts over the short study period. To maximize study efficiency and resource utilization these subjects will not be enrolled unless necessary.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by PI. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed

consent form will be in the possession of the Investigator before the study is initiated. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and FDA CDER all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	SCREENING VISIT 1 (Screen)[a]	**STUDY1 VISIT 2 (Baseline)[a]**	**STUDY2 VISIT 3 (Month 3)[a]**	**STUDY3 VISIT 4 (MONTH 6)**
Informed Consent	**X**			
Medical History	**X**			
Complete Physical Exam	**X**			
Abbreviated Physical Exam		**X**	**X**	**X**
Height	**X**			
Weight	**X**			
Vital Signs	**X**	**X**	**X**	**X**
Pregnancy Test (Serum)	**X**			
Hematology	**X**		**X**	**X**
Chemistry	**X**			**X**
Research blood stored	**X**	**X**	**X**	**X**
Neurological + ophthalmological exam with neurologist		**X**	**X**	**X**

MRI		**X**	**X**	**X**
Randomization	**X**			
Dispensing of Study Drug		**X**	**X**	
Counting of Returned Study Drug				**X**
Initiate Subject Diary	**X**			
Subject Diary Review		**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**
Additional cognitive assessments		**X**	**X**	**X**
OCT	**X**	**X**		**X**
VEP	**X**	**X**	**X**	**X**
Vision testing (high, low contrast)		**X**	**X**	**X**
Cone contrast		**X**	**X**	**X**
VFQ		**X**	**X**	**X**
Questionnaires (MFIS, MSWS12, SF-36)		**X**	**X**	**X**
Assess likely side effects		**X**	**X**	**X**
EDSS		**X**	**X**	**X**
SDMT		**X**	**X**	**X**
Timed walking tests		**X**	**X**	**X**
ERG** (optional)	**X**			

Safety phone call at Week 6.

** **In rare cases during the initial visit, the patient may be asked to undergo an electroretinogram. This test measures the electrical response of the eye's light-sensitive cells, called rods and cones. These cells are part of the retina (the back part of the eye). This test is used to detect disorders of the retina. For this study, this option exists only to be used in cases where more information is needed to confirm a diagnosis of optic neuritis. The test is performed by placing numbing drops in the patient's eyes, so that there is no discomfort. Then, the patient's eyes are held open with a small device called a retractor. An electrical sensor (electrode) is placed on each eye and the electrical activity of the retina is recorded in response to light. The primary risk associated with the study is a temporary scratch of the surface of the cornea due to the electrode. Otherwise, there are no risks associated with this procedure.