Treatment of progressive forms of Multiple Sclerosis with pulsed ACTH (Acthar gel)

Adam F. Carpenter*, Susan Scarberry, and Bhupendra Khatri*****

* **University of Minnesota (Minneapolis, MN)**
** **Sanford Neurology (Fargo, ND)**
*** **Ascension/Wheaton Franciscan Healthcare (Milwaukee, WI)**

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List of Abbreviations

ACTH - adrenocorticotropic hormone
AE - adverse effect, or adverse event
AI - ambulation index
BRB-N - Brief Repeatable Battery of Neuropsychological tests
CMP - comprehensive metabolic panel
CTCAE - Common Terminology Criteria for Adverse Events
DEXA - dual-energy X-ray absorptiometry
DSMB - Data Safety Monitoring Board
EDSS - expanded disability status scale
FDA - Food and Drug Administration
GEE - generalized estimating equation
HgbA1C - hemoglobin A1C
FSS - Fatigue Severity Scale
IDS - Investigational Drug Services
IRB - Institutional Review Board
LCVA - low-contrast visual acuity
MN - Minnesota
MP - methylprednisolone
MS - multiple sclerosis
MSFC - Multiple Sclerosis Functional Composite
MSWS-12 - Multiple Sclerosis Walking Scale
ND - North Dakota
OCT - optical coherence tomography
PASAT - Paced Auditory Serial Addition Test
PPMS - primary progressive multiple sclerosis
PRMS - progressive relapsing multiple sclerosis
RNFL - retinal nerve fiber layer
SAE - serious adverse event
SDMT - Symbol Digit Modalities Test
SPMS - secondary progressive multiple sclerosis
SRT - Selective Reminding Test
RRMS - relapsing remitting multiple sclerosis
T25FW - timed 25 foot walk
WI - Wisconsin
WLG - Word List Generation
10/36 - 10/36 Spatial Recall Test
6MWT - Six minute walk test
9HP - 9-hole Peg Test

1. Abstract

We propose investigating the safety, tolerability and efficacy of adrenocorticotropic hormone (ACTH, Acthar gel) administered as a pulsed regimen consisting of injections on three consecutive days per month in patients with progressive forms of multiple sclerosis (MS). Safety and tolerability will be assessed by subject-reported adverse events as well as vital signs, physical examination, serologic tests and radiographic measures of bone mineral density. Efficacy will be assessed by changes in walking speed over the course of the study, with the primary endpoint a comparison of the proportion of subjects exhibiting a 20% worsening in the Timed 25-Foot Walk Test (T25FW). We will also explore the effects of ACTH on slowing neurological deterioration via several measures of disability in these patients, including effects on ambulation, cognition, fatigue, vision, and global measures of disability. Finally, we will measure the effect of pulsed ACTH on changes in retinal nerve fiber layer thickness, to assess an important paraclinical measure of neurodegeneration. Because degenerative changes occur at a slow pace, a 3 year study is proposed.

2. Background

MS has both neurodegenerative and inflammatory aspects *(1-4)*
. In secondary progressive MS (SPMS), the degenerative aspect predominates but inflammation persists, particularly in the early stages, in the form of both occasional acute inflammatory relapses and chronic low-level white matter inflammation. Primary progressive MS (PPMS), by definition, has no clinical relapses but there are MRI abnormalities indicative of inflammation and pathological studies show changes very similar to those seen in SPMS.

While great progress has been made in treating relapsing-remitting MS, t**here are no proven safe and effective treatments for progressive forms of MS**. No treatment has been shown to benefit patients with PPMS. The only treatment that has been shown to provide some benefit in SPMS is chemotherapy; the approved immunomodulatory treatments (β-interferons, glatiramer acetate, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate) have not been proven to slow disease progression in this phase of the disease *(5)*. Cyclophosphamide and mitoxantrone have both been shown to slow progression in SPMS, particularly in its early stages, but have obvious disadvantages in terms of toxicity *(6-10)*.

β-interferons, natalizumab, fingolimod, teriflunomide and dimethyl fumarate have all been shown to slow progression in relapsing-remitting MS, presumably due to their anti-inflammatory properties. However, a recent study *(11)* of the long term effects of β-interferons showed no reduction in the progression of disability as measured by the time to reach sustained Expanded Disability Status Scale (EDSS) 6.0, suggesting that the benefit seen in the short term studies is not maintained. Corticosteroids may also slow the progression of disability accumulation in patients with RRMS, at least in one study. Zivadinov et al. *(12)* conducted a 5 year study of RRMS patients comparing pulsed methylprednisolone (MP) administered for 5 consecutive days every 4 months with MP administered only as needed for clinical relapses. In subjects receiving regular pulsed

MP there was a significant reduction in brain atrophy compared with those receiving steroid treatment for relapses alone. The pulsed MP group also showed a significant clinical benefit; EDSS in treated patients improved from 2.1 at outset to 1.7 at completion while in controls the EDSS declined from 2.4 to 3.4. A phase II study of pulsed MP in secondary progressive MS showed a benefit of high dose (500 mg) over low dose (10 mg) MP in time to onset of sustained progression of disability, but no difference in the proportion of patients who experienced sustained disability progression *(13)*.

ACTH is FDA-approved for treatment of MS relapses, infantile spasms, and multiple non-neurologic disorders. ACTH has both corticotropic and neurotropic properties *(14)*, and has the potential to benefit both the inflammatory and neurodegenerative aspects of MS, respectively. Because of its corticotropic properties, long term use may result in steroid-related adverse effects (AE's). Administration of steroids as a pulsed regimen has been generally found to be well tolerated with few of the usual AEs associated with chronic corticosteroid use *(12)*, although reduction in bone mineral density has been reported *(15)*. The multiple mechanisms of ACTH action may offer advantages over steroids alone for the treatment of MS. Any slowing of progression resulting from treatment of progressive forms of MS with ACTH could be due to its corticotropic effects, its neuroprotective effects, and/or corticosteroid-independent effects on the immune response *(16)*. A recent preliminary report evaluating pulsed ACTH versus pulsed MP as an add-on to interferons for treatment of RRMS found a significant benefit of pulsed ACTH (compared to pulsed MP) in reducing relapses over one year *(17)*.

3. Hypotheses

1. ACTH administered as a monthly pulse (consisting of three consecutive days of subcutaneous injection) will be safe and well-tolerated in progressive MS patients.
2. Pulsed ACTH treatment will slow the progression of sustained physical disability of ambulation, as measured walking speed (T25FW), walking endurance (6 minute walk test, 6MWT), the Hauser ambulation index (AI), and the MS walking scale (MSWS-12), all validated measures related to ambulation in MS patients.
3. Pulsed ACTH treatment will slow the progression of sustained cognitive disability as measured by the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), a measure of cognitive impairment that has been specifically validated for MS.
4. Pulsed ACTH treatment will reduce the proportion of subjects who show a sustained progression of the EDSS over the course of the study. (EDSS is a validated measure of overall MS disability).
5. Pulsed ACTH will reduce the decline in retinal nerve fiber layer thickness as measured by optical coherence tomography (OCT).

4. Inclusion and Exclusion Criteria

1. Inclusion criteria:
    a. Male or female patients with a confirmed diagnosis of MS by McDonald criteria *(18)*.
    b. Age ≥ 18 years.
    c. SPMS, PPMS, or PRMS (progressive relapsing MS) phenotype, according to Lublin and Reingold criteria *(19)*.
    d. EDSS 2.0-6.0, inclusive.
    e. Able to understand the consent process.

2. Exclusion criteria:
    a. Known intolerance of ACTH or corticosteroids.
    b. Diabetes mellitus, defined as pre-existing diagnosis, fasting blood glucose > 125 mg/dl, or glycosylated hemoglobin ≥ 6.5%, or 2-hour blood glucose > 200 mg/dl in an oral glucose tolerance test.
    c. Osteoporosis, defined as pre-existing diagnosis or T-score on dual-energy X-ray absorptiometry (DEXA) scan of ≤ -2.5 in any of the following regions: left femoral neck, left total hip, right femoral neck, right total hip, L1-L4 (combined score).
    d. Current serious medical condition which may interfere with subject's ability to complete the study, or for which pulsed ACTH therapy is contraindicated or might complicate current therapy (e.g. cancer, severe psychiatric illness, chronic infections, autoimmune disorders).
    e. Treatment with cytotoxic broad-spectrum immunosuppressive agents (including but not necessarily limited to mitoxantrone, cyclophosphamide, alemtuzumab, or cladribine) within 3 years prior to randomization or during study participation.
    f. Treatment with non-cytotoxic broad-spectrum immunosuppressive agents (including but not necessarily limited to corticosteroids, ACTH, azathioprine, mycophenolate mofetil, or methotrexate) within 3 months prior to randomization or during study participation.
    g. Treatment with FDA-approved MS disease-modifying therapies (β-interferon, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, daclizumab or ocrelizumab) will be permitted. Treatment with these medications should be ongoing and stable for at least 3 months prior to randomization. Starting, stopping, or changing MS disease-modifying medications during the study is discouraged.
    h. Treatment with natalizumab will be permitted, as long as treatment has been ongoing and stable for at least 3 months prior to randomization and JC virus antibodies are negative. Subjects taking natalizumab should be tested for JC virus antibodies every 6 months during the study (per standard of care), and if JC virus antibodies become positive, then the subject must either discontinue natalizumab or withdraw from the study.
    i. Treatment with rituximab will be permitted, as long as treatment has been ongoing and stable for at least 3 months prior to randomization.

j. Treatment with dalfampridine or compounded 4-aminopyridine will be permitted as long as treatment has been ongoing and stable for at least 3 months prior to randomization. Starting or stopping dalfampridine during study participation is strongly discouraged.
k. Stimulant medications for fatigue (such as methylphenidate, modafinil, armodafinil, amantadine or dextroamphetamine) will be permitted, but subjects will be asked to not take these medications on study visit days until all study procedures/assessments are completed.
l. Women who are pregnant, planning to become pregnant over the course of the study, or breastfeeding.
m. Concurrent participation in another study involving the use of blinded investigational drug.

3. Pre-screening considerations
    a. Pre-screening for osteoporosis and diabetes: Since the study budget does not contain funds to cover the cost of screen failures, it is recommended that subjects be pre-screened for osteoporosis and diabetes, e.g., with a DEXA scan and diabetes screening test (fasting blood glucose, glycosylated hemoglobin, or oral glucose tolerance test) within 2 years prior to the screening visit. Whether or not to order these pre-screening tests (or to omit them at the risk of an uncompensated visit in the case of screen failure) will be left to the discretion of the local PI.
    b. Dalfampridine: Since most patients with progressive MS with EDSS 2.0-6.0 have some walking impairment, it follows that most will be candidates for treatment with dalfampridine (or other aminopyridine preparation). While this is permitted within the study, starting or stopping dalfampridine (or other aminopyridine) during the course of the study should be avoided, as this may confound the ambulation outcome measures in the study. It is recommended that for all patients, consideration of whether or not they should be treated with dalfampridine be done prior to enrollment. For subjects interested in enrolling and who have not had a trial of dalfampridine (and are deemed an appropriate candidate for this medication), a trial of dalfampridine is recommended to see if they benefit from it. Once the determination is made whether or not to continue dalfampridine, they may enroll in the study once they have been stable on (or off) dalfampridine/aminopyridine for 3 months.

5. Outcome measures

A. Ambulation

Walking impairment is a signature characteristic of MS, and of progressive MS in particular. Estimates of the prevalence of gait impairment in MS range from approximately 40-80%, and MS patients rate walking difficulties as one of the most burdensome aspects of the disease *(20)*. Multiple walking assessment methods have been developed and evaluated in MS, including the gait-specific measures included in the present study: the 6MWT *(21)*, the T25FW *(22)*, the MSWS-12 *(23)* and the AI *(24)*.

There is no clear "best" objective assessment of ambulation in MS. The most commonly used metrics are the EDSS (an overall measure of MS-related disability that is heavily "weighted" toward walking ability) and the T25FW. The T25FW is, as the name implies, a timed measurement of how fast a patient can safely walk 25 feet. Thus, it is primarily a measure of walking *speed*. In contrast, the 6MWT (a measure of the distance a subject can walk in 6 minutes) is a test of walking *endurance*. While impairments in walking speed certainly may cause problems in daily living for MS patients (e.g. crossing the street, getting to the bathroom on time), impairments in walking endurance probably account for the majority of walking-related functional limitations in MS. Several studies have evaluated and compared these metrics, and found both to be valid and reliable *(25, 26)*. These studies found high correlations between walking speed and walking distance, but recommended a test of walking distance such as 6MWT be included in intervention studies where ambulatory function in an important outcome (as in the present study) *(25)*. The 6MWT is more likely to capture the effect of motor fatigue on walking ability than is the T25FW, and is likely less susceptible to floor effects from subjects with no (or mild) gait impairment *(27)*.

The literature contains much more data on T25FW than on 6MWT in MS patients. In particular, there is no published data on the change in 6MTW in MS patients over time. Therefore, change in the T25FW will serve as the primary endpoint of the study. Multiple studies have found that a change of 20% from baseline T25FW is both reliably detectable and clinically meaningful *(28-31)*. **The primary endpoint of this study will be the proportion of subjects in each treatment arm who show a 20% increase in T25FW at the last study visit, compared to baseline.** Changes in 6MWT, MSWS-12, and AI will be secondary endpoints.

B. Safety and Tolerability

A key outcome measure of this phase II study is the safety and tolerability of pulsed ACTH compared to placebo. Little background information on adverse effects of pulsed ACTH in MS is available. A preliminary report of a one-year study *(17)* reported generally no increase in adverse effects in MS subjects receiving pulsed ACTH compared to pulsed MP, and fewer "psychiatric episodes" in the ACTH group. Potential AEs of concern are primarily those related to corticotropic effects, i.e. common steroid-related AEs such as increased risk of infection, weight gain, glucose intolerance, osteoporosis, hypertension, fluid retention, electrolyte derangements, and mood or behavioral changes.

Safety and tolerability of ACTH will be assessed in three ways: via volunteered responses from subjects regarding AEs, by elicited responses regarding specific symptoms, and by laboratory and physical exam measures. The advantage of volunteered (unsolicited) responses is that they allow unexpected AE's to be assessed and tend to highlight more serious or distressing AEs, while elicited responses have the advantage of more sensitive detection of specific AEs of interest *(32)*. The volunteered responses will be obtained by an investigator or study coordinator at each follow-up visit, asking the

subject "Have you had any medical problems since your last visit?" Responses will be recorded on a log and severity will be rated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Subjects may also report AE's by phone, and these will be rated and logged in a similar manner. Study personnel will contact subjects monthly (by phone, email, etc.) around the time of their scheduled study drug injections, to remind them of the injections and to check for any new AE. If a phone-reported AE is deemed serious or possibly serious, an unscheduled visit will be arranged to allow the local investigator to assess the AE more fully (see section 7E, Unscheduled Study Visits). Elicited responses will be assessed through a questionnaire that will explore insomnia, irritability, dyspepsia, injection pain, edema, dysgeusia, fatigue, vision, skin changes, and changes in menstruation.

Physical exam and laboratory measures will include objective measurements of weight, blood pressure, skin changes, edema, myopathy, cataracts, glucose, electrolyte abnormalities, bone mineral density (DEXA) and hepatic toxicity.

The following events are considered protocol-defined AEs and should be recorded on the AE log:

1. Weight gain: 5% increase compared to baseline
2. Increased blood pressure: increase of >20mm systolic or 10mm diastolic compared to baseline
3. Increased A1c: absolute increase of 1% or greater from baseline (Screening visit value) that is sustained across 2 consecutive measures
4. Hypokalemia: any potassium value below the lower limit of normal
5. New Osteopenia (compared to Baseline): DEXA T score between -1 and -2.5
6. Osteoporosis: DEXA T score less than -2.5
7. A DEXA T score drop of ≥ -0.5 during the study

As is typical, the study will not be powered based on safety and tolerability measures because AEs are anticipated to be rare and because the type and severity of AEs may be unpredictable. **The main secondary endpoint for safety and tolerability will be a comparison of the number of serious adverse events (SAE) over the study period in the ACTH group versus the placebo group**. A SAE will be considered any event with a score equal or greater than 3 on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. AEs receiving a mild or moderate grade will also be compared between the two treatment groups.

C. Cognition

Cognitive dysfunction is ubiquitous in MS, affecting an estimated 40-70% of patients *(33)*, and is a major cause of disruption in daily and occupational function in MS patients *(34)*. The most common domains of cognitive impairment in MS are memory, processing speed, visuospatial functions, verbal abilities, sustained attention and

executive function *(35)*. The BRB-N is a set of five cognitive tests developed by National MS Society's Cognitive Function Study Group as a research tool to detect cognitive changes in MS patients and to evaluate the effect of treatment interventions on cognition *(36)*. The five neuropsychological tests comprising the BRB-N were chosen for their ability to assess the cognitive domains most frequently impaired in MS in a practical time period (20-30 minutes). The BRB-N includes the Selective Reminding Test (SRT, a test of verbal learning and delayed recall), the 10/36 Spatial Recall Test (10/36, visuospatial learning and delayed recall), the Symbol Digit Modalities Test (SDMT, sustained attention and processing speed), the Paced Auditory Serial Addition Test (PASAT, sustained attention and processing speed) and Word List Generation task (WLG, verbal fluency).

Relatively little published data exists on the evolution of BRB-N over time in progressive MS patients, but available data suggest that study durations longer than 2 years are needed to observe changes in cognition. Huijbregts et al. *(35)* found stable BRB-N performance over 2 years in 30 SPMS and 25 PPMS patients. Montalban and colleagues conducted a 2 year study of interferon β1b or placebo in PPMS, and administered the BRB-N at baseline, at 2 years, and at 5 years. No change in any of the BRB-N tests was evident in the placebo group at 2 years *(37)*, but at 5 years the placebo group showed significant deterioration in the SDMT, 10/36 and WLG (but not in the PASAT or SRT) *(38)*.

The tests will be administered according the BRB-N manual *(36)*, including order of test administration, instructions to subjects, testing procedures, and scoring. Because practice effects may occur with neuropsychological tests, one practice administration of the BRB-N will be performed in each subject as recommended in the BRB-N manual. The practice session will be performed either during the screening visit or, if the screening and baseline visits are combined, the BRB-N will be performed twice during the baseline visit, with the second BRB-N administration serving as the baseline. The PASAT can be administered with either a 2-second or 3-second interval between successive digits; the 3-second version will be used in this study. Multiple versions of each test are provided with the BRB-N, to control for learning effects with repeated application of identical test material (15 versions each for SRT, 10/36, SDMT and WLG, and 2 versions for PASAT). These different versions are constructed to be equivalent, but some authors have found significantly different scores between different versions of certain tests *(39)*. We will administer the BRB-N variants sequentially (version 1 at the training session, version 2 at baseline, version 3 at year 1 follow-up visit, etc.) for the tests with 15 versions, and will alternate versions A and B on successive administration of the PASAT. Applying the same versions to all subjects at each visit, combined with the randomized design, should control for confounding or bias due to any systematically different performance (difficulty) between the test versions, and prevents confounding due to learning effects.

D. Vision

Low-contrast visual acuity (LCVA) is a sensitive measure of visual impairment in MS patients *(40)* and has been recommended for incorporation into the Multiple Sclerosis Functional Composite (MSFC). LCVA is correlated with retinal nerve fiber layer thickness as measured by OCT *(41)* (see section 5.F., below). Visual acuity will be measured in each eye separately as well as binocularly, at three contrast levels (100%, 2.5%, and 1.25%) using low-contrast Sloan letter charts (Precision Vision, LaSalle IL). For each measurement, the number of letters (maximum = 70) correctly identified will be recorded. Changes in LCVA over the study, and correlation of LCVA measures with OCT measures, will be exploratory outcomes of the study.

E. Fatigue

Fatigue is an extremely common symptom in MS patients, and often one of the most disabling. Over 50% (and up to 90%) of MS patients cite fatigue as a significant problem *(42)*. The Fatigue Severity Scale (FSS) is a validated, patient-reported metric of fatigue symptoms that was specifically developed for MS and related disorders *(43)*. The FSS will be administered to all study subjects at baseline and at each annual follow-up. The change in FSS from baseline to study end will be compared between treatment arms, as an exploratory endpoint. Many MS patients are treated with stimulant medications (such as methylphenidate, modafinil, or amphetamine preparations) for fatigue symptoms, and such medications (and the timing of their dosing) could obviously affect FSS scores, as well as other study measures. Accordingly, subjects will be asked not to take such stimulant medications on study visit days (although they will be advised to bring such medications with them, so that they may take them as needed after the study assessments are completed).

F. Global Measures of MS-related disability (EDSS and MSFC)

The EDSS and the MSFC are the two most commonly used metrics for assessing neurologic disability in MS. The EDSS is a 19-step ordinal scale between 0 and 10 based on exam findings or symptoms in 8 functional systems plus ambulation. Despite some well-known limitations (e.g. only moderate intra- and inter-rater reliability, overweighting of ambulation, insensitivity to change at certain levels), it remains the gold standard for assessing disease and disability status in MS. Most current clinical trials in MS evaluate "progression of disability" as an increase in EDSS score that is sustained across multiple measures. Because higher EDSS scores rely more heavily on changes in ambulatory function and generally become less sensitive to change than lower scores, a larger "step" change from baseline EDSS is often required for lower baseline EDSS than for higher baseline EDSS in order to constitute progression of disability. In the current study EDSS will be measured at screening and at annual follow-up visits for the three year study duration, by a neurologist or nurse practitioner certified in EDSS evaluation. The same examiner will perform all EDSS evaluations in an individual subject, if possible. Use of a backup examiner (if trained and certified in EDSS) will be permitted in cases where the primary

examiner is unavailable. Progression of disability will be defined as an increase from baseline EDSS of ≥ 1.0 for baseline EDSS of 2.0-5.0, or an increase of 0.5 for baseline EDSS of 5.5-6.0. **The proportion of subjects in each treatment arm who exhibit progression of disability will serve as a secondary endpoint.** Due to the limited number of EDSS assessments, an increase in EDSS score will not have to be "sustained" across multiple assessments in order to be considered evidence of disability progression.

The MSFC *(22, 44)* was developed by a National MS Society task force on clinical outcomes in MS. It consists of 3 objective measures (tests) covering three functional domains: leg function and ambulation (the T25FW), arm and hand function (the 9-hole Peg test, 9HP), and cognitive function (the PASAT). The individual scores on each test are converted to Z-scores, and the Z-scores averaged into a single MSFC Z-score *(44)*. **Change in overall MSFC Z-score (and in each individual Z-score) over the course of the trial will be compared between treatment arms, and will constitute secondary endpoints.**

It should be noted that 1) the T25FW is utilized both as a stand-alone measure (and primary endpoint) and as a component of the MSFC, and 2) the PASAT is a component of both the MSFC and of the BRB-N (see section 5D, above). At each annual follow-up visit, the MSFC and the PASAT will be administered once to each subject, with the single score or measurement for that visit contributing to all relevant metrics (i.e., the PASAT will not be administered once for the BRB-N and then again for the MSFC). Previous studies have found practice effects in the 9HP and PASAT, but not the T25FW*(45, 46)*, with the practice effects stabilizing after the third administration. Accordingly, three practice sessions of the PASAT and 9HP will be administered prior to the baseline tests. Since the PASAT is one of the components of the BRB-N, and one practice session of the entire BRB-N will be administered, two additional practice sessions of the PASAT will be administered at the screening or baseline visit. The MSFC tests will be administered according to the MSFC manual *(44)*, including test order, instructions to subjects, testing procedures, number of repetitions, and scoring.

G. Optical Coherence Tomography (OCT)

Retinal nerve fiber layer (RNFL) thickness will be measured by OCT, an accurate and reproducible measure of the integrity of unmyelinated axons in the retina *(47, 48)*. RNFL thickness is reduced in MS patients compared to controls, and reduction in RNFL correlates with visual function impairment in MS patients *(49)*. The reduction in RNFL thickness is most prominent in eyes that have experienced a prior episode of optic neuritis (ON), but even eyes that have not suffered past episodes of ON show a reduction in RNFL compared to healthy controls *(50)*. This latter fact makes OCT an attractive candidate for monitoring neurodegenerative processes in MS, which may underlie the gradual neurologic decline in progressive forms of MS. To date, limited longitudinal studies of OCT in progressive MS have been performed *(51)*, but this remains a potentially very powerful surrogate marker for MS progression and the effect of treatments. Recently, alternative OCT measures such as macular volume and the

thickness of retinal layers other than the RNFL (e.g. the ganglion cell layer) have been shown to be abnormal in MS, and possibly to differentiate between the different MS phenotypes *(52)*.

Each subject will have OCT performed on each eye at baseline and then annually for 3 years (total of 4 OCT per subject). OCT will be performed on the Spectralis OCT system (Heidelberg Engineering, Germany) using the glaucoma protocol set. If the study center's available Spectralis OCT system has the neurology-oriented "N-site" software, then the RNFL scan (see below) will be obtained twice, once using the glaucoma protocol set and once using the axonal (N-site) protocol set. Pupillary dilation will not be routinely performed, as it is usually unnecessary for OCT *(49)*. If dilation is deemed necessary to achieve adequate OCT quality (e.g., due to cataract), the subject may be excluded from the OCT portion of the study. Alternatively, dilation may be performed (with typical mydriatic eye drops) if the dilation and OCT are done after the other functional study assessments (e.g. EDSS, MSFC, LCVA, BRB-N) during the study visit, or if dilation/OCT are done on a separate visit day within a +/- 2 week window of other efficacy measures. In other words, pupillary dilation for OCT purposes will not be allowed to interfere with the other efficacy assessments that require vision for their performance.

Up to three different scans will be performed on each eye at each visit, to assess RNFL thickness macular volume, and individual retinal layer thickness (ganglion cell layer, inner nuclear layer, etc). The RNFL scan will be obtained twice (once using the glaucoma protocol and once using the axonal protocol) if the axonal protocol is available. The axonal protocol (N-site) is optimized for detecting abnormalities in MS, and is thus the preferred method. However, all of the study sites are not expected to have access to the axonal protocol, while all will have the glaucoma protocol available. Therefore, we will obtain all scans on the glaucoma protocol (to ensure consistency of data), and acquire the axonal protocol RNFL scan as well when it is an option. The scans to be obtained are:

i. **RNFL scan (circle scan)** – Standard settings for peripapillary RNFL with the Spectralis glaucoma protocol will be used: 12 degree (3.45 mm) circular scan manually centered on the optic disc, ART = 100, circle = 12°, 768 A-scans.

ii. **Macular volume scan (posterior pole scan)** – The posterior pole scan from the glaucoma protocol set will be used, again using the standard settings: 30x25, 61 sections, 760 A-scans per section, distance between B-scans = 120 μm, ART = 9.

iii. (optional) **RNFL scan (circle scan) using N-site software** – Standard settings for peripapillary RNFL with the Spectralis axonal protocol will be used: 12 degree (3.45 mm) circular scan manually centered on the optic disc, ART = 100, circle = 12°, 768 A-scans.

For each scan, minimum quality score is 20 (with a goal quality score of ≥ 25). If a quality score of ≥ 20 cannot be obtained, data from that scan will not be included for analysis. The individual centers/technicians obtaining the OCT will evaluate only for quality of the OCT scans (i.e., no

formal clinical interpretation of the OCT results will be performed. The image alignment eye-tracking system (TruTrack, Heidelberg Engineering, Germany) will be utilized throughout.

Data submitted from each OCT session will include printouts of all RNFL scans, plus electronic files (.e2e format) containing each of the 2 (or 3) scans.

If a study site does not have access to the Spectralis OCT system, a different spectral-domain high-resolution OCT system such as Cirrus HD-OCT (Zeiss) may be used as an alternative, with similar scans acquired (RNFL scan, macular volume/posterior pole).

Change in thickness of the temporal quadrant peripapillary RNFL over the course of the study will be a secondary study endpoint. Exploratory endpoints will include changes in macular volume and changes in other RNFL regions (e.g. superior, inferior, nasal, and global).

6. Statistical Issues and Data Analysis

A. Study Design

The study design is a randomized, double-blind, placebo-controlled, multi-center, phase II clinical trial.

B. Sample Size Calculation

The main objective of the study is to investigate the safety and tolerability of pulsed ACTH in progressive MS patients over three years. The primary efficacy endpoint of the study is the proportion of subjects exhibiting a 20% increase (worsening) from baseline in the T25FW. No baseline data are available regarding the rate at which a pooled population of progressive MS (i.e., SPMS, PPMS and/or PRMS) patients experience 20% increase in T25FW. However, Bosma et al. *(53)* evaluated change over 2 years in all three components of the MSFC (T25FW, 9HP, and PASAT) in 191 PPMS patients, and found that 45% of patients showed a 20% or greater increase in T25FW. This data was used as the basis for sample size considerations, with the following assumptions:

The findings in PPMS patients *(53)*

1. will generalize to a mixed sample of any progressive MS phenotype.
2. Extrapolated to a 3 year follow up period, 60% of progressive MS patients will show a 20% or greater increase in T25FW.

Utilizing a significance level of 0.05 and equal sample sizes, 42 subjects per treatment arm would provide 80% power to detect a 50% difference in the proportion of subjects reaching the threshold of 20% worsening in T25FW (P1 = 0.6, P2 = 0.3, $\alpha = 0.05$, $\beta = 0.2$, 2-sided test). Given the length of the study, we anticipate a dropout rate of up to 10-20% of randomized subjects. To account for this possibility, a total sample size of 100 subjects (50 per treatment arm) will be randomized.

C. Randomization

The study will utilize blocked randomization stratified by study center, with equal (1:1) allocation to the ACTH and control groups.

D. Blinding

Study subjects, their referring physicians, the study monitor, and all study personnel who come in contact with study subjects (including site principal investigators, examining neurologists, study coordinators, nurses, and other study staff and their designated backups) will be blinded to treatment allocation. One investigator who will not come in direct contact with study subjects (Dr. Parry) as well as the study statistician and other members of the Data Safety Monitoring Board (DSMB, see section 7F) will be unblinded, to allow for assessment of any safety concerns that may arise over the course of the study.

E. Data Analysis Plan

Descriptive analyses of baseline characteristics and all outcome measures (primary and secondary) will include means with standard deviations or medians with ranges for continuous variables depending on the parametric or non-parametric distribution of the variables, and frequencies with percentages for categorical variables. Between group (ACTH and placebo) comparisons of baseline characteristics and baseline outcome measures will be done using two sample t-tests or Wilcoxon rank sum tests for parametric and non-parametric continuous variables, respectively, and Chi-square tests or Fisher's exact tests for categorical variables.

Models will adjust for age, gender, and MS phenotype; EDSS and disease duration will be included as covariates if significant in preliminary models. Interactions between treatment group and MS phenotype will be tested in each model; if significant, treatment effect will be evaluated in models stratified by MS phenotype.
The possibility of mid-study therapy regimen change for some subjects (see Exclusion criteria g. and h.) will be accounted for in analysis by running models with and without these subjects to explore the impact of these changes on analysis results. If results from the two models are consistent, all subjects will be included in the final model.
There are multiple distinct outcomes of interest in this study; since each outcome measures a unique aspect of MS progression no adjustment for multiple comparisons is planned.

Primary endpoint:

Between group differences in the odds of a 20% or greater increase in T25FW, the primary outcome measure of clinical progression of MS, will be tested at 36 months using multiple logistic regression models adjusted for covariates. Generalized

estimating equation (GEE) models will be used to test for between group differences in change over time in clinical progression (20% or greater increase in T25FW) adjusted for covariates. To test for between group differences in time to clinical progression distribution curves, Cox proportional hazards models (conditional on model assumptions being met) or Kaplan-Meier analysis will be used.

Secondary endpoints:

Safety and tolerability
To evaluate safety and tolerability of ACTH, lists and descriptive statistics of adverse events, serious adverse event, and treatment compliance will be compiled and calculated for each group at each visit. Fisher's exact tests will be used to test for between group differences in specific adverse event rates, serious adverse event rates, and treatment compliance rates.

Between group differences in mean changes in physical exam and laboratory measures (weight, blood pressure, HgbA1c, bone mineral density) will be tested using two-sample t-tests. In addition, between group differences in the proportion of subjects with abnormal blood pressure, HgbA1C, electrolyte and bone mineral density levels will be tested using Chi-square tests or Fisher's exact tests.

Change in ambulation, cognition, and global measures of MS-related disability scores
Between group differences in study endpoint mean of each of the secondary outcomes: change in ambulation (6MWT, MSWS-12, Hauser Ambulation Index), change in cognition (eight subtests of the five BRB-N tests), and change in MSFC z-scores will be tested using multiple linear regression models adjusted for baseline score and other covariates. Mixed model analysis of repeated measures, utilizing data collected at all time points, will be used to test for between group differences in change over time in mean secondary outcome measures adjusted for covariates. Between group differences in the odds of EDSS progression will be tested using multiple logistic regression models adjusted for other covariates. Generalized estimating equation (GEE) models will be used to test for between group differences in change over time in progression rates adjusted for other covariates. Cox proportional hazards models (conditional on model assumptions being met) or Kaplan-Meier analysis will be used to test for between group differences in time to EDSS progression.

OCT Temporal Quadrant RNFL
OCT temporal quadrant RNFL measurements from one eye per subject will be used for analysis purposes; randomly selected unless the patient has a history of optic neuritis in which case the unaffected eye will be selected. Between group differences in change in OCT temporal quadrant RNFL thickness will be tested using a multiple linear regression model adjusted for baseline thickness and other covariates. Multiple linear regression models will also be used to test for between group differences in three year rate of change adjusted for other covariates. Separate mixed model analyses of repeated

measures will be used to test for between group differences in 1) change over time in RNFL thickness and 2) change over the 3 years in annualized rates of RNFL change.

Exploratory endpoints

Fatigue

Between group differences in study endpoint mean FSS will be tested using a multiple linear regression model adjusted for baseline FSS score and other covariates. Mixed model analysis of repeated measures, utilizing data collected at all time points, will be used to test for between group differences in change over time in mean FSS adjusted for covariates.

Other vision measures

Multiple linear regression models will be used to test for between group differences in LCVA scores adjusted for other covariates. Binocular LCVA scores will be used to test for a treatment effect on vision changes; monocular LCVA scores will be used for correlation with OCT measures (from the matching eye). Generalized estimating equation (GEE) models will be used to test for between group differences in change over time in vision loss rates adjusted for other covariates. In addition correlation of LCVA with OCT measures (RNFL and macular volume) will be evaluated using Pearson correlation analysis (Spearman correlation will be used if measures have skewed distributions).

Between group differences in mean OCT macular volume scan measures will be tested using multiple linear regression models adjusted for covariates. mixed model analyses of repeated measures will be used to test for between group differences in change over time in OCT macular volume measures.

7. Study Procedures

A. Schedule of study procedures:

1. Symptoms questionnaire for subjective adverse events at baseline, 3, 6 and 12 months and then annually.
2. Comprehensive metabolic panel (CMP) and hemoglobin A1C (HbgA1C) at screening, 6 and 12 months, and then annually.
3. EDSS and DEXA scan (both hips/femurs and lumbar spine) at screening and then annually.
4. OCT at baseline and then annually.
5. MSFC, T25FW, 6MWT, LCVA, MSWS-12, AI, FSS and BRB-N at baseline and then annually.
6. Practice sessions (at screening visit:
    a. BRB-N - 1 practice session

b. PASAT - 2 practice sessions (in addition to the one administered during BRB-N)
c. 9HP - 3 practice sessions

Table 1. Study Schedule

	V1 Screen 0 to -4 wks	**V2** Baseline M0	**V3** *** M3	**V4** M6	**V5** M12	**V6** M18	**V7** M24	**V8** M30	**V9** M36
Informed Consent	X								
Inclusion/Exclusion	X								
Injection Training		X							
Blood Pressure		X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X
Safety Lab Tests[a]	X			X	X		X		X
Skin & Edema Assessment		X	X	X	X	X	X	X	X
OCT		X			X		X		X
LCVA		X			X		X		X
EDSS	X				X		X		X
Timed 25-Ft Walk		X			X		X		X
9-Hole Peg Test	XXX	X			X		X		X
PASAT (apart from BRB-N)	XX								
6 Minute Walk Test		X			X		X		X
MS Walking Scale - 12		X			X		X		X
Fatigue Severity Scale (FSS)		X			X		X		X
Hauser Ambulation Index		X			X		X		X
Brief Repeatable Battery	X	X			X		X		X
DEXA Scan[b]	X[c]				X		X		X
Randomization		X							
Symptom Questionnaire		X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X
Unsolicited Adverse Events			X	X	X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X	X	
Return Drug Vials and Logs			X	X	X	X	X	X	X

[a] Safety lab tests: comprehensive metabolic panel and hemoglobin A1C.
[b] Bilateral hips and lumbar spine
[c] DEXA scan may be omitted at the Screening Visit if subject provides results of DEXA scan done within the 3 months prior to the Screening Visit

*** The month 3 visit is primarily a safety visit to assess AEs and to assess any difficulties subjects may be having with study drug injections. No laboratory tests are done, and no physical exam other than the skin and edema assessment (which would be unlikely to yield abnormal findings at 3 months, since chronic steroid side effects would likely take longer to occur in the 3 day per month pulsed dosing). For patients traveling a long distance to the study, this visit might be much more conveniently done by phone. **While the preference is for the month 3 visit to be done on-site**, it can (optionally) be done as a phone visit, e.g. for subjects who 1) are inconvenienced by coming in person for this visit, and 2) have prior experience with taking subcutaneous injections. If this option is chosen, then 1) 6 months' worth of study drug (rather than 3) must be given out at the baseline visit, 2) no study drug dispensing or drug return will occur at the month 3 visit, and 3) no skin and edema assessment will be done at the month 3 visit.

B. Treatment Administration:

ACTH (Acthar gel) and placebo will be provided by the funding sponsor and distributed to individual sites. The study medication will be self-administered at a dose of 80 units subcutaneously for 3 consecutive days every month for the duration of the study. The dose will be reduced to 40 units if the full dose cannot be tolerated. Specific training in the injection procedure will be done prior to the initial injection.

C. Study Staff

Each study site will have a local principal investigator (Fargo, Dr. Scarberry; Minneapolis, Dr. Carpenter; Milwaukee, Dr. Khatri; other sites may be added in the future) who will oversee study operation at that site and be responsible for the acquisition and handling of study data according to the procedures outlined in this protocol. Each site will utilize a study neurologist or neurology nurse practitioner certified in EDSS administration, who will perform the EDSS, review safety and tolerability data and report AEs and SAEs. There will not be a separate "treating" and "examining" neurologist at each site. A backup study neurologist may be designated, in case the primary study neurologist is unavailable for a scheduled visit. Other study staff such as research coordinators or nurses may be assigned to assist in recruitment, scheduling, and study procedures. Study coordinators/nurses may administer all study assessments except the EDSS and the physical examination (e.g., MSFC, BRB-N, 6MWT, MSWS-12, AI, LCVA, and subject-reported AE assessments), as long as they have been specifically and adequately trained on administering these assessments. Alternatively, the site study neurologist (or backup) may administer these assessments as well. OCT and DEXA scans will be performed by operators trained in administering those tests. A study monitor will be designated from the primary study site (University of Minnesota, Minneapolis) and will oversee data collection and management, as well as visit all study sites to review compliance with study procedures.

D. Relapses

Patients with certain forms of progressive MS (SPMS, PRMS) may experience acute disease relapses in addition to gradual neurologic decline. MS relapses entail new or worsened

neurologic symptoms that typically evolve over days, last for weeks, and gradually improve. They commonly manifest as focal deficits in sensory and/or motor function, visual disturbance, brainstem/cerebellar symptoms (such as vertigo, diplopia or ataxia), bladder or bowel symptoms, gait impairment, or fatigue. Acute cognitive or behavioral symptoms are less common, but may occur. Relapse symptoms may eventually resolve completely, partially, or not at all.

This study is not designed to assess the effect of ACTH on MS relapses, but the occurrence of relapses could affect the study in several ways. First, relapse symptoms could affect study measures of neurologic function/disability (T25FW, EDSS, etc. – any of the study metrics could be affected), either because the study visit occurred during the relapse or because the relapse resulted in incomplete recovery. Second, relapse symptoms (or signs) could be reported (or interpreted by study investigators) as AEs. Third, relapses are commonly treated with short courses of corticosteroids, and side effects from corticosteroid therapy could be mistaken for or confounded with AEs related to study medication. While relapses are expected to be quite rare in the study population, due to these potential impacts on study measures it is important to identify the occurrence and timing of relapses and corticosteroid treatment in study subjects. This will be done via the following procedures:

1. Subjects will be instructed to contact their treating neurologist (who may or may not be a study investigator) if they think they may be experiencing an MS relapse.
2. Subjects will also be asked to notify their study contact (site study coordinator or investigator) to inform them of the possible relapse, including the nature of symptoms, date of symptom onset, presence of any concomitant medical illness (e.g. upper respiratory tract infection, urinary tract infection, recent surgery or trauma), and any other special circumstances. The study coordinator will enter this information on the Potential Relapse case report form.
3. Evaluation of the potential relapse will be done by, and at the discretion of, the subject's treating neurologist.
4. The subject will be asked to provide copies of the treating neurologist's clinic notes and/or other medical records related to the possible relapse (e.g., MRI reports) to study staff.
5. The local principal investigator will review the medical records and judge whether or not the subject experienced a relapse. This will be recorded on the Potential Relapse case report form (as Relapse or Not Relapse).
6. Treatment of the relapse or suspected relapse (e.g., with corticosteroids) will be allowed, at the discretion of the treating neurologist. The dates, dose and formulation of treatment will be reported to the study coordinator and logged on the Potential Relapse case report form.

E. Unscheduled Study Visits

Subjects will be asked to contact their study site if they develop new symptoms that are concerning to them. The local study coordinator will record the reported symptoms on the Unsolicited AE Form, which will be reviewed by the local investigator. An unscheduled study visit will occur if the local investigator deems these AEs as potentially serious, possibly related to study medication, and/or requiring in-person assessment. If the reported symptoms are interpreted as mild and/or unrelated to study medication, the subject may be referred to their primary physician or advised to report back by phone with updates about symptom

evolution/resolution. Unscheduled visits will not be routinely performed for suspected MS relapse (see section 7D, Relapses), although they may occur in this situation if the reported symptoms are interpreted as a possible treatment-related AE. Assessments/procedures performed at an unscheduled visit will include all of the assessments done at Visit 3 (see Table 1) with the exception of study drug distribution; any further assessments and/or procedures (e.g. physical examination, other tests, referrals) will be done at the discretion of the local investigator.

F. Early Termination and Intent to Treat

Once subjects are randomized, regardless of if or the length of time they have been on blinded treatment, they will be included in the efficacy (intent to treat) analysis if efficacy data are available (that is, if they have completed at least one annual follow-up visit). Subjects who withdraw (e.g., due to side effects) prior to completing the Month 12 visit will be asked to return the study drug to the site, and to participate in annual phone calls (Months 12 and 24), and to return to the site for the final visit at Month 36. Subjects who withdraw after completing the Month 12 visit will be asked to return the study drug to the site, and to complete the remaining annual study visits (i.e., Month 24 and Month 36) even though they are not receiving drug. Subjects are of course allowed to decline further participation, in which case they would be considered lost-to-follow-up.

G. Data Safety Monitoring

A DSMB will be formed and will consist of one MS specialist, one neurologist familiar with the evaluation and treatment of MS but not otherwise associated with the study, and the study biostatistician. A DSMB chairperson will be chosen from one of the two neurologists on the DMSB.

Safety data will be reviewed by the DSMB at 6 and 12 months and then annually, starting from the time the first subject receives a dose of study medication and ending at participant study completion (i.e., no active participants on study drug and enrollment closed). Reports from all DSMB meetings will be forwarded to the Institutional Review Board (IRB). Any SAEs or unexpected AE's reported at other times will be reviewed by the head of the DSMB and reported to other members of the DSMB if considered significant enough to warrant interim review by the full committee. In the event of unanticipated SAEs that reflect new or increased risk to the subjects and are considered possibly related to the study medication or procedures (UPIRTSO) the funding sponsor and all study sites will be notified within 48 hours of the local investigator learning of the event. The local IRB will be notified within that IRB's policy timelines (e.g., the University of Minnesota IRB will be notified within 10 business days). A detailed analysis of all AEs will be conducted at the end of the first year of the study. The efficacy measures will also be analyzed annually throughout the study to see whether any signal of benefit is appearing. However, the study will be terminated only if there are unacceptable adverse events, not because of lack of any efficacy signals since it may take the entire 3 year duration of the study for any

beneficial effect to become manifest. Study termination due to safety concerns will be at the discretion of the DSMB; no pre-specified stopping rules will be used.

8. Cytokine sub-study

There are multiple mechanisms by which melanocortins such as adrenocorticotropic hormone (ACTH) might alter the course of multiple sclerosis (MS) in a beneficial way *(16, 54)*. One such mechanism is altering the balance between pro-inflammatory and anti-inflammatory cytokines via direct immunomodulating effects of melanocortins on immune system cells. A sub-study will be performed (at the University of Minnesota site only) to evaluate the change in plasma cytokine levels in subjects receiving ACTH compared to those receiving placebo, in order to better elucidate the possible mechanisms of ACTH in MS.

Subjects enrolling in the main study at the University of Minnesota site will be invited to participate in the plasma cytokine sub-study as well. Subjects who enroll in the sub-study will, at the annual study visits when they have blood drawn for safety blood tests, have additional blood tubes drawn for the cytokine analysis (2 EDTA tubes). Tubes will be mixed, centrifuged, and then plasma aliquoted and stored at -80° C. Leukocytes (buffy coat) will also be aliquoted and mixed with RNA*later* (a reagent that stabilizes RNA for future possible analysis of gene expression) and stored at -80° C. Leukocytes or whole blood samples will also be stored for possible future DNA analysis. The potential future RNA and DNA analyses are not currently planned as part of the sub-study, and subjects may opt out of this aspect (i.e. choose not to have genetic material stored) in the consent form.

Cytokine levels will be assessed with multiplex cytokine assays on the Luminex system, and will be performed by the Cytokine Reference Laboratory at the University of Minnesota. Approximately 25-30 analytes (cytokines, chemokines, growth factors, etc) will be measured. The current list of analytes planned for the study include: Eotaxin, FGF-2, G-CSF, GM-CSF, IFNa2, IFNg, IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, IP-10, MCP-1, MIP-1a,b, TNFa, VEGF, M-CSF, and MIG. Assays will be performed in batches of 40 samples (in duplicate) at a time; thus each "batch" would correspond to 10 subjects worth of samples (10 subjects x 4 samples/subjects = 40 samples). We anticipate the total number of subjects to be enrolled in the sub-study to be between 30 and 80. Differences between the active (ACTH) and placebo groups for plasma levels of each analyte will be assessed with multiple linear regression models adjusted for covariates (e.g. age, gender, MS phenotype) and/or mixed model analyses of repeated measures.

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