STUDY TITLE:	The Effect of ACTH (Acthar®) on Measures of Fatigue in Patients with Relapsing Multiple Sclerosis
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A. SPECIFIC AIMS

This is a multi-center, randomized, double-blind, placebo-controlled study to demonstrate the safety, tolerability, and effect of ACTH on fatigue in patients with relapsing multiple sclerosis (RMS). The primary objective of this study is to assess the efficacy of ACTH versus placebo in reducing fatigability in patients with RMS. Secondary objectives include assessment of the tolerability and safety of twice-weekly ACTH treatment vs. placebo and evaluation of ACTH on depression, sleepiness, and quality of life measures and correlations between these measures.

B. BACKGROUND AND RATIONALE

With the advent of disease modifying therapies that reduce the risk of worsening physical disability, the importance and impact of excessive fatigue on quality of life in patients with MS has come into clearer focus. Quality of life (QOL)-altering fatigue has been reported to occur in as many as 92% of patients with MS, for many patients constituting the most important source of disability. Furthermore, there is a strong association between fatigue and clinical depression, suggesting shared pathophysiological mechanisms and/or anatomic substrates for these two important symptomatic features of MS.

Fatigue may result from sleep disturbances due to frequent nocturia, restless legs syndrome, sleep apnea or weakness-induced hypoventilation, as well as pain from nocturnal muscle spasms, and central neuropathic pain syndromes. Other contributors may include hypothyroidism, cardiac or pulmonary disease, medication side effects, and depression. However, a large number of patients with MS have what we will refer to as Primary MS Fatigue (PMSF), the cause(s) of which are unknown, but which appears to be the direct result of MS-induced CNS impairment. Typically, such MS patients report that despite awakening well-rested and not fatigued, they develop severe physical and /or mental fatigue that may be disabling and preventing them from any further activity, even in the absence of excessive exertion, and, at times, with rapid or sudden onset. Resting or sleeping repeatedly will restore energy levels for short intervals, and patients may be compelled to spend the day taking frequent naps.

It is evident that PMSF bears little or no relationship to the degree of physical impairment (Flachenecker et al., 2002; Murray, 1985) in all but the most extreme cases of physical disability (Mills & Young, 2010). There is a strong correlation with clinical depression, which also fails, in many cases, to correlate with degree of physical disability, and suggests the possibility that they share common pathophysiological mechanisms. When other potential fatigue-induced confounders are eliminated, there remain a large number of MS patients with severe, excessive fatigability, and it is these patients, who we refer to as having PMSF. Although the neurogenic mechanism(s) of PMSF are not understood, and the success at pharmacologic management has been extremely limited (Brown, Howard, & Kemp, 2010; Lange, Volkmer, Heesen, & Liepert, 2009; Moller et al., 2011; Murray, 1985; Pucci et al., 2007), earlier studies have suggested that dysregulation of the hypothalamic-hypophyseal axis, and the CNS limbic system, as well as impaired ACTH and corticosteroid release, may contribute to fatigue in patients in MS. Furthermore, pro-inflammatory cytokines, which are up-regulated in patients with MS, are known to produce fatigue. As an example, the pro-inflammatory cytokine IL-6, up-regulated in MS and up-regulated following interferon administration, is reduced following corticosteroid administration. Corticosteroid-induced reduction of IL-6 following interferon treatment has been associated with reduction in fatigue in patients with MS (Kumpfel et al., 2007). Thus, one potential mechanism by which ACTH might reduce PMSF is an increase in circulating corticosteroid levels. However, direct effects of ACTH, mediated via CNS melanocortin receptors, may influence fatigue, as well as affective state. Lastly, there are no therapeutic agents for the treatment of PMSF that have demonstrated significant efficacy, and the development of a significant therapeutic agent for fatigue in MS would profoundly affect large numbers of patients with MS.

The proposed study is a randomized, placebo-controlled, double-blinded trial to evaluate the efficacy, safety, and tolerability of 80 units of ACTH versus placebo given subcutaneously twice every week for 6 months for the treatment of fatigue in patients with RMS.

The ACTH dosage chosen falls well within the range routinely employed, with efficacy, for treatment of MS relapses. It is known that this dose is well-tolerated, with an excellent safety profile. We have selected a 6-month treatment interval, which has become the standard phase II trial duration for multiple sclerosis therapeutic agents. This duration should also provide adequate time to study time of onset of effects of ACTH upon fatigue and whether they sustained over at least several months of medication use.

The primary endpoint of this study is a statistically significant reduction of fatigue in subjects who have RMS and fulfill the definition of PMSF when treated with ACTH compared to placebo. Known biological actions, both directly and indirectly, of ACTH upon the CNS make it a plausible candidate agent for the reduction of PMSF.

The secondary endpoints are: 1) statistically significant improvement in patient self-assessment of quality of life; 2) statistically significant reduction in patient self-assessment of depression; 3) statistically significant reduction in patient self-assessment of sleepiness measures when treated with ACTH, as compared to placebo, and 4) the safety and tolerability of twice weekly ACTH injections compared to placebo. The rationales for the secondary endpoints are: 1) the demonstration that quality of life improvements with ACTH use in patients with PMSF would increase the clinical significance or ACTH-induced reduction in PMSF; 2) fatigue and depression are so strongly correlated in patients with MS that reduction in depression with ACTH treatment would strengthen the possibility that depression and fatigue share, at least in part, a common mechanism, and a parallel decrease in depression would strengthen the validity of the potential causative action of ACTH upon fatigue; 3) sleepiness is strongly correlated with MS-induced fatigue and thus reduction in daytime sleepiness would be an additional measure of validity for ACTH-induced reduction in MS-induced fatigue; 4) ACTH use, although demonstrated to be safe in treating patients with MS, is being used on a twice-weekly basis over a 6 month period, which is a regimen that has not been previously employed, to our knowledge, in MS patients.

C. RESEARCH DESIGN AND METHODS

Study Design

The proposed study is a 28-week randomized, placebo-controlled, double-blind trial comparing the efficacy of ACTH versus placebo for the treatment of fatigue in patients with RMS (RMS). Ninety patients with RMS who meet all of the eligibility criteria will be enrolled from five participating sites. Eligible patients will be consented by site investigators or delegated research personnel before undergoing any study procedures. Subjects will be randomized to ACTH or placebo at 1:1 ratio.

Endpoints

The primary objective of this study is to assess the efficacy of ACTH versus placebo in reducing fatigability in patients with relapsing MS. The primary endpoint is a statistically significant reduction of fatigue measured by MFIS and FSS, which will be administered at baseline, week 8, 16, 24, and 28.

Secondary objectives include assessment of the tolerability and safety of weekly ACTH treatment vs. placebo and evaluation of ACTH on depression, sleepiness, and quality of life measures and the correlations between measures. The secondary endpoints are measured by BDI-II, ESS, SF-36 at baseline, week 8, 16, 24, and 28. Clinical and laboratory adverse events (AE) and serious adverse events (SAE) will be monitored continuously during the study period to capture safety and tolerability information.

Patient Recruitment

Patients with stable (no relapses for the previous 90 days) relapsing form of MS, being treated with interferon beta1a or 1b, glatiramer acetate, fingolimod, dimethyl fumarate or teriflunomide for at least 6 months, with Expanded Disability Status Scale (EDSS) scores of 4 or less, Modified Fatigue Impact Scale (MFIS) score of 38 or greater, or a Fatigue Severity Scale (FSS) score of 36 or greater, Beck Depression Inventory-II (BDI-II) score of 19 or less, and Epworth Sleep Score (ESS) of 9 or less. Subject will be excluded if he or she has attempted suicide in the past, has current suicidal thinking based on the Columbia Suicide Severity Rating Scale (C-SSr), or is preparing for suicide. History must be negative for difficulty sleeping, sleep apnea, painful nocturnal spasms, nocturnal neuropathic pain, and restless leg syndrome, history of psychosis or neuroleptic use, have no evidence of current hypothyroid state, use of cannabis, opiates, benzodiazepines, or other gaba-ergic medications except baclofen or tizanidine. Subjects cannot have received corticosteroids of any type for 90 days prior to baseline visit. Subjects must not have any of the contraindications for Acthar Gel as listed in the approved label, including sensitivity to proteins of porcine origin. Subject must agree not receive any live or live-attenuated vaccine during the trial. Ninety subjects will be recruited and randomized 1:1 to receive ACTH or placebo in a subject and examining physician-blinded manner. The sample size was calculated by a power analysis for a two-sided test with alpha= 0.5 and power = 0.80 and assuming a 20% dropout rate.

Subjects will be randomized in groups of 4, with equal number of placebo and ACTH treated patients in each 4-subject group. In order to reach enrollment target in 12 months, full competitive enrollment will be applied until the enrollment goal is fulfilled.

The study protocol, informed consent forms (ICF), and case report forms (CRF) must be approved by the organization's institutional review board or appropriate ethics committee. Site investigators will obtain written informed consent to participate from eligible patients prior to screening or any study procedures taking place. A copy of the ICF will be given to the patient and the original ICF and the documentation of the consent process will be kept in the patient's record at each site.

Inclusion Criteria

Candidates must fulfill **all** of the following criteria before being included in the study:

1. Have documented diagnosis of Relapsing MS as defined by McDonald Criteria 2011 Revision for at least 6 months
2. Age range of 18 to 65 years old, inclusive at time of screening
3. Have been treated with interferon beta 1a or 1b, glatiramer acetate, fingolimod, dimethyl fumarate or teriflunomide for at least 6 months, with reported adherence rate of at least 75%, at time of screening
4. Have an EDSS score of 0 to 4, inclusive
5. Have MFIS $\geq$ 38 or FSS $\geq$ 36, BDI-II $\leq$ 19, and ESS $\leq$ 9
6. Women of childbearing potential must employ proven methods to prevent pregnancy during the course of the trial
7. Able to understand the purpose and risks of the study
8. Must be willing to sign an inform consent
9. Must be willing to follow the protocol requirements
10. Subject must agree not to receive any live or live-attenuated vaccine during the trial

Exclusion Criteria

Candidates will be excluded from study entry or participation if **any** of the following exclusion criteria exist at any time during the study:

1. Have any of the contraindications for Acthar Gel as listed in the approved label, including sensitivity to proteins of porcine origin.
2. Had treatment of systemic or oral corticosteroids of any type in 90 days prior to baseline/randomization
3. Had a relapse or documented objective neurologic worsening in 90 days prior to baseline/randomization
4. Has concurrent neurological disease other than multiple sclerosis
5.
    a. Any history of sleep apnea
    b. History (within the last 90 days) of nocturnal pain and/or nocturnal spasms that interferes with or interrupts sleep, or uncontrolled nocturnal restless leg syndrome
6. History of psychosis, bipolar disorder, mania/hypomania
7. History of coronary heart disease, congestive heart failure, chronic pulmonary disease, emphysema, anemia, bleeding disorder, gastrointestinal bleeding, intestinal ulcer, clinically significant cardiac arrhythmia, Type I or II diabetes, uncontrolled hypertension, seizure disorder, cardiac arrhythmia, immune deficiency disorder, HIV-AIDS, tuberculosis, or dysthyroidal state (patients with a history of hypothyroidism or hyperthyroidism, which has been corrected to physiological levels will not be excluded)
8. History of substance abuse, other than tobacco within the past 5 years or current alcohol dependence
9. Current use of cannabis, opiates, benzodiazepines, barbiturates, gabapentin, pregabalin, topiramate, divalproex sodium, carbamazepine, oxcarbazepine, or any gaba-ergic medications other than tizanidine or Baclofen, which are permitted for spasticity treatment
10. History of any malignant neoplasm except for past basal cell or squamous cell carcinoma of the skin, that has been successfully treated prior to the screening visit
11. History of psychosis or history of use of neuroleptics including, but not restricted to, haloperidol, chlorpromazine, aripiprazole, olanzipine, resperidone
12. History of suicide attempt, current suicidal thinking or is preparing for suicide
13. Current use of Amphetamines or methylphenidate
14. Current use of modafinil, or armodafinil
15. Current use of amantidine
16. The subject must have had a medication-free interval of:
    a. 7 days for prior use of:
        i. methylphenidate, amphetamine or dextrophetamine
        ii. modafanil or armodafinil
        iii. diphenhydramine, phenylephrine, loratidine
        iv. gabapentin, pregabalin, topiramate, valproate/divalproex
        v. oxcarbazepine
        vi. codeine, hydrocodone, oxycodone
    b. 14 days for prior use of:
        i. Desloratidine
        ii. Amantidine
        iii. alprazolam, lorazepam
        iv. morphine, hydromorphone
    c. 28 days for prior use of:
        i. clonazepam
        ii. cannabis or other cannabinoids
    d. 90 days for prior use of carbamazepine

17. Women who are pregnant or who intend to attempt pregnancy during the time of their enrollment in the trial
18. Women who are breastfeeding
19. Any other factor, which in the opinion of the investigator, renders the patient inappropriate for this trial
20. Subjects currently enrolled in a clinical trial utilizing an investigational agent

Concomitant medications

Allowed concomitant medications:

- FDA-approved sleeping medications, at their approved doses

Prohibited concomitant medications:

- Same as in Exclusion Criteria # 8, 9, 11, 13, 14, 15
- Live or live-attenuated vaccines

Discontinuation of Subjects from the Study

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

Participation in the study will be terminated if any of the following situations occurs:

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

2. Patient has an adverse event that presents unacceptable risk judged by the investigator

3. Patient has inadequate adherence to the protocol

4. Patient is lost to follow-up

5. Patient becomes pregnant

Treatment Overview

Dosage and Administration of Acthar® or matching placebo

The study drug (ACTH 40 units or identical-appearing placebo) will be given subcutaneously twice weekly for 2 weeks. If the patient tolerates this dosage regimen, the dose will be increased to 80 units or placebo twice weekly. If the 80 unit dosage is not tolerated, the dosage will be reduced to 40 units twice weekly for the remainder of the 24 week participation. The weekly doses will be given 3 days apart, for example, on every Monday and Thursday or every Tuesday and Friday. Patients are not allowed to take doses on consecutive days. If a patient cannot take a dose on a scheduled day, the dose can be taken either a day early, or a day late. Patients that forget to take their scheduled dose will be encouraged to take their dose the following day.

Randomization/Treatment assignment and blinding

A total of 90 patients will be randomized either to active drug (ACTH), or placebo in a 1:1 ratio stratified by study site. Each study site will be assigned a site number, and each patient who signed consent form and received a screening test will have a unique study ID, which identifies the patient and the study site at which they participate throughout the study. Within each site, subjects will be randomized in blocks of 4, 2 ACTH and 2 placebo treated patients, to achieve balance in the allocation of subjects to study drug versus placebo arms. The order in which each of the 4 samples is selected will be predetermined by a

computer generated randomization schedule. Medications will be labeled and distributed by the coordinating site. The study drugs and matching placebo will be packaged in the same way using identical appearing vials. A unique random number will be printed on the label for each package. A master list containing drug kit numbers and drug assignment (ACTH or placebo) will be kept in a password-protected computer file in the coordinating site pharmacy. Each study site will be required to assign patients in the order of the randomization schedule and dispense medications according to the medication kit numbers indicated on the predetermined randomization schedule. The investigators, study coordinators/nurses, and subjects will remain blinded to randomization assignment until study completion, and the blind will only be violated if, in the judgment of the treating physician, unblinding is necessary for patient safely in the setting of a serious adverse event. The DSMB will not be blinded.

Drug Administration and Storage Instructions

The study drug is supplied in a 5 mL multi-dose vial containing 80 USP units per ml.

Patients will be instructed to inject 40 units subcutaneously twice a week for the first two weeks and 80 units twice a week thereafter, with 3 days between the two doses. Three vials of ACTH will be dispensed at baseline, and 4 vials will be dispensed at Week 8 and Week 16. Each subject is to return used and unused vials, along with their injection log, at each follow-up visit, before they receive their next allotment of drug. Investigational drug use will be recorded in the accountability log by the study coordinator/nurse at each site, and the unused vials will be retained until they are returned to the central coordinating center.

Laboratory Testing and Study Procedure

Review of medical history, physical exam, Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), Epworth Sleepiness Scale (ESS), Beck Depression Inventory-II (BDI-II) and Expanded Disability Status Scale (EDSS) will be performed at screening to assess the eligibility of the patient, and the Columbia-Suicide Severity Rating Scale will be administered. The outcome measures, including MFIS, FSS, BDI-II, ESS, and SF-36, will be administered at baseline, week 8, week 16, week 24, and week 28 which is 4 weeks after the last ACTH or placebo dose. In addition, office visits with the treating physician will be conducted at the same interval for physical exam, review of concomitant medications and adverse events, and monitoring of patient safety and eligibility, and administration of the C-SSR. Laboratory tests will be performed at the time of study visits. A separate serum sample (7 ml SST tube) will be collected at baseline, week 16, and week 28. This sample will be stored at -20c until shipped to the coordinating center. The specimen will then be stored at the study coordinating center for future research use.

STUDY FLOWCHART

ACTH for MS fatigue							
	Screening	Baseline	Follow-up Evaluations				Premature Termination
Visit #	1	2	3	4	5	6	
Week	-4 to -1	0 (±4days)	8 (±4days)	16 (±4days)	24 (±4days)	28 (±4days)	
Informed Consent & Demographics	X						
Randomization		X					
Medical & Neurological History	X	X	X	X	X	X	X
Physical & Neurologic Exam	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
ECG	X						
Laboratory Assessments							
• Urinalysis	X	X	X	X	X	X	X
• CBC	X	X	X	X	X	X	X
• CMP	X	X	X	X	X	X	X
• TSH	X						
• Pregnancy Test/HCG (for female only)	X	X	X	X	X		
Additional Serum Sample for Research Purposes		X		X		X	
EDSS	X						
MFIS, FSS, BDI-II, ESS, SF36	X	X	X	X	X	X	X
C-SSR	X	X	X	X	X	X	X
Study Drug Dispensing		X	X	X			
Protocol Compliance & Study Drug Accountability		X	X	X	X	X	
Concomitant Therapy and AEs	Monitor and record throughout the study						

Informed consent

The investigator or designated research staff will obtain informed consent from each subject after explaining the purpose of the study and the potential risks and benefits known or can be reasonably expected. The IRB approved informed consent form will be signed by the subject or the legal representative before the subject participates in any study procedure. The original signed informed consent form will be kept in the subject's medical record, a duplicate will be provided to the subject.

Visit 1 or Screening visit (Week -4 to -1; 7 to 28 days prior to Baseline)

The following clinical and laboratory evaluations will occur within 4 weeks prior to baseline. The investigator/treating neurologist (or designee where allowed) must perform all screening evaluations to determine patient eligibility.

- Informed consent
- Demographics
- Review of medical and neurological history
- Review of medications
- Vital signs
- Physical and neurological exam
- EDSS
- ECG
- Laboratory assessments: Urinalysis, CBC, CMP, TSH, Pregnancy test/HCG (female only)
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Visit 2 or Baseline visit (Week 0; 4 weeks after Screening +/- 4 days)

The following clinical and laboratory evaluations will occur at baseline visit, which must be completed 4 weeks after screening (+/- 4 days). The investigator/treating neurologist will review inclusion/exclusion criteria to confirm patient eligibility before study drug is dispensed.

- Randomization
- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC Urinalysis, CMP , Pregnancy test/HCG (female only)
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Study drug dispensing
- Protocol compliance study drug accountability
- Concomitant therapy and AEs
- Additional serum sample for research purposes

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Visit 3/Week 8 (8 weeks +/- 4 days from baseline)

The following clinical and laboratory evaluations will occur 8 weeks after baseline with a +/- 4 day window. The investigator/treating neurologist will review inclusion/exclusion criteria to confirm patient eligibility before study drug is dispensed.

- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC, Urinalysis, CMP, Pregnancy test/HCG (female only)
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Study drug dispensing
- Protocol compliance study drug accountability
- Concomitant therapy and AEs
- Additional serum sample for research purposes

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Visit 4/Week 16 (16 weeks +/- 4 days from baseline)

The following clinical and laboratory evaluations will occur 16 weeks after baseline with a +/- 4 day window. The investigator/treating neurologist will review inclusion/exclusion criteria to confirm patient eligibility before study drug is dispensed.

- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC, Urinalysis, CMP, Pregnancy test/HCG (female only)
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Study drug dispensing
- Protocol compliance study drug accountability
- Concomitant therapy and AEs
- Additional serum sample for research purposes

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Visit 5/Week 24 (24 weeks +/- 4 days from baseline)

The following clinical and laboratory evaluations will occur 24 weeks after baseline with a +/- 4 day window. The investigator/treating neurologist will review inclusion/exclusion criteria to confirm patient eligibility.

- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC, Urinalysis, CMP, Pregnancy test/HCG (female only)
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Protocol compliance study drug accountability
- Concomitant therapy and AEs

- Additional serum sample for research purposes

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Visit 6/Week 28 (28 weeks +/- 4 days from baseline)

The following clinical and laboratory evaluations will occur 28 weeks after baseline with a +/- 4 day window.

- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC, Urinalysis, CMP
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Protocol compliance study drug accountability
- Concomitant therapy and AEs
- Additional serum sample for research purposes

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Premature termination visit

If discontinuation of study drug occurs, a premature termination visit must be performed as soon as possible, or within 7 days after the last dose of study drug. Randomized patients who were withdrawn from the study for any reason will not be replaced. The following clinical and laboratory evaluations will be performed:

- Interval medical and neurological history
- Vital signs
- Physical and neurological exam
- Laboratory assessments: CBC, Urinalysis, CMP
- MFIS, FSS, BDI-II, ESS, SF36, C-SSR*
- Concomitant therapy and AEs

* The C-SSR must be reviewed by the site principal investigator or treating physician prior to the patient leaving the clinic

Unscheduled visits

Patients may be asked to return for unscheduled visit to assess any undesired clinical, or laboratory changes that occur during the study.

Study withdrawal

If a patient is lost to follow-up after all means of contact have been attempted, she/he will be withdrawn from the study.

Patient Monitoring and Evaluation

Patients will be instructed to contact their treating neurologist immediately in the event of a relapse.

A Stage 1 safety and efficacy analysis will be performed when 45th subject has completed visit 4(week 16). This analysis will be performed by the unblinded clinical and biostatistician members of the data safety monitoring board (DSMB). While this analysis is being performed, no new subjects may enroll in the investigation, but treatment of those already enrolled will continue while the analysis is taking place. If more subjects in the placebo arm demonstrate 20% or greater improvement than in the ACTH arm on both the MFIS and FSS, the study will be halted and subjects in the study will cease receiving investigational agents. If the ACTH arm is equal or superior to the placebo arm in MFIS and/or FSS, the study will continue, as will recruitment of the additional 45 subjects. If the study is halted due to lack of efficacy after the Stage 1 analysis, an additional analysis for efficacy will be performed utilizing those subjects who completed 6 months enrollment at the time the study was halted.

Treatment compliance

Patients will be instructed to complete a medication administration log and return the logs to study coordinator at each visit. Information on missed doses and total number of missed doses will be captured. Missing more than 2 doses in an 8-week interval is considered non-compliant. The investigator will discuss the medication regimen with non-compliant patients and they will be encouraged to continue with their injection schedule.

Potential Pitfalls and Contingencies

This study requires self-administration of an injectable agent. Thus there is a risk of non-compliance on the part of the subjects either due to needle phobia, intolerance to injections or lapse memory on the part of the subjects.

Data Processing and Analysis

Data forms will be faxed to the data coordination center within 3 business days after each study visit and processed by staff trained in data entry procedures. The forms will be entered by two staff working independently. The completeness of the data and whether the data values are in an appropriate range will be checked periodically. Study sites will be asked to complete data clarification requests for confirmation of missing data or questionable information.

Statistical/Analytical Plan

Primary endpoint

Statistical analysis will be performed to test the change from baseline to end of study in two fatigue measures (MFIS and FSS) to be completed by patient at baseline, Week 8, Week 16, Week 24, and Week 28.

Secondary endpoint

Statistical analysis will be done to test the change from baseline to end of study in depression, sleepiness, and quality of life measures (BDI-II, ESS, and SF-36) to be completed by patient at baseline, Week 8, Week 16, Week 24, and Week 28.

All AEs are to be coded and grouped by organ system. AEs will also be tabulated by severity and by relationship and summarized by treatment group. Summary tables of the AEs will be presented to show the incidence and frequency by treatment group and by study site.

Statistical method

This study will collect longitudinal data that consists of repeated measures on each individual. The mixed-effects regression model for the analysis of longitudinal data will be used to test the changes of the fatigue scores over time.

Sample Size Justification

Ninety subjects will be recruited and randomized 1:1 to receive ACTH or placebo in a subject and examining physician-blinded manner. If the MFIS score decreases from 38 for about 20% with standard deviation =16.4 in the 45 patients who received ACTH, the power to reject the null hypothesis in a paired t-test with alpha= 0.5 would be 86%. If the difference of the changes of MFIS score between two treatment group is 7.6 with within group standard deviation=16.4 in the 90 patients, the power to reject the null hypothesis in a t-test with alpha= 0.5 would be 87%. Ziemssen and colleagues (Ziemssen, Hoffman, Apfel, & Kern, 2008) studied the effect of glatiramer acetate on fatigue in MS patients. Glatiramer acetate was found to be associated with a reduction in absence from work and a significant reduction in fatigue symptoms, as measured by MFIS. The data from Ziemssen et al. were used for the sample size calculation for this study.

D. REGULATORY, SAFETY AND MONITORING

Members and Responsibilities of DSMB

There will be 3 members of the DSMB, one will be a clinical neurologist with expertise in the treatment of patients with MS, one will be a PhD level biostatistician with past experience in statistical analysis of clinical studies of MS and one will be a physician with adequate expertise in endocrinology. The DSMB will review all adverse events (including all MS relapses) that occur during the study, independently conduct the interim analysis, the timing of which as described above, and the final analysis for safety and efficacy of the investigational treatment. The DSMB will also meet at any time they may choose if there are concerns for patient safety. Records of all committee reviews and input will be kept in the study binder.

Regulatory Requirements

The study will be performed in accordance with ICH GCP Guidelines and the Code of Federal Regulations for clinical research. Any amendments to the study protocol must be approved by Providence IRB and the IRB/IEC of each site before implementation. AEs and protocol violations or deviations must be reported according to the guideline of the IRB/IEC of each site.

Safety Assessments

Physical Examination

A full physical examination will be conducted at every visit. Any worsening or new abnormality that is clinically significant is to be recorded as an AE and will be analyzed as such. MS related symptoms are not to be reported as AEs unless, in the opinion of the investigator, the symptoms are unusually serious and relevant.

Vital Signs

Vital signs including body temperature, pulse, respiration rate, systolic and diastolic blood

pressure, and weight will be obtained at every visit

12-lead ECG

A 12-lead standard ECG will be performed at screening visit.

Clinical Laboratory Parameters

The following laboratory assessments will be performed at the local laboratory at selected visits:

- CBC
- Urinalysis
- CMP
- TSH
- Pregnancy Test (for female subjects only)

Adverse Event

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

Serious Adverse Events

A serious adverse event (SAE) is defined as any event that:

- Results in the outcome of death
- Places the subject at immediate risk of death (a life-threatening event)
- Results in a congenital anomaly/birth defect
- Results in hospitalization or prolongs an existing hospitalization
- An event that results in persistent or significant disability/incapacity.
- Require intervention to prevent permanent impairment or one of the other outcomes listed in the definition above.

Adverse Event Recording/Reporting

All adverse events (including pre-dosing and treatment-emergent) should be recorded in the subject's Adverse Event CRF regardless of severity or relationship to study drug. The investigator must review the laboratory findings and sign and date the laboratory report. Any moderate or severe laboratory abnormalities should be reported to the coordinating center as outlined below. All SAEs must be reported by the investigator to Providence Regional Research/ Regulatory office by email at mark.schuster@providence.org or fax to 503-215-6547 within 24 hours of the investigator's knowledge of the event. Providence Health & Services will report SAEs to the FDA. All SAEs must be recorded on SAE forms and be reported, whether or not the event is considered by the investigator to be related to study drug.

Severity

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

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

Relationship to Study Drug

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

Not related	Any event that does not follow a reasonable temporal sequence from administration of investigational drug AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely	Any event that does not follow a reasonable temporal sequence from administration of investigational drug *OR* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Possibly	Any reaction that follows a reasonable temporal sequence from administration of investigational drug *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Related	Any reaction that follows a reasonable temporal sequence from administration of investigational drug *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

Investigator Reporting Responsibilities for Safety and Monitoring

- Monitor and record all adverse events
- Determine the seriousness, causality, and severity of each adverse event
- Report all serious adverse events to the FDA according to the Code of Federal Regulations

- Report to the Sponsor within 24 hours (non-Providence Health & Services sites)
- Actively and persistently pursue follow-up of serious adverse events
- Forward a copy of the follow-up information to Sponsor

E. ESTIMATED DURATION OF THE STUDY AND CRITICAL TIMELINE ELEMENTS

I. Please complete expected/estimated dates:

Table 1: Critical Timeline Elements	
Element Name	**Date**
IRB approval, expected	9/30/2013
IND submission, expected	9/30/2013
Study start date, estimated	10/01/2013
Enrollment completion date, estimated	9/30/2015
Study completion date, estimated	7/31/2016

II. Describe publication plan and anticipated number of abstracts and manuscript submissions (include intended conference(s) for presentation and month, year of conference(s)):

Upon completion of data collection, a research abstract will be submitted to the next American Academy of Neurology or Consortium of Multiple Sclerosis Centers annual meeting. Upon completion of the study, a research manuscript will be submitted to Neurology, Neurotherapeutics, or the Journal of Multiple Sclerosis.

F. REFERENCES

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G. BUDGET

Budget must be approved *by institution prior to submission. To ensure Questcor IIS resources are used effectively- we require that all budgets: 1) have itemized direct study costs; 2) do not exceed 30% in overhead (indirect) costs. The (itemized) proposed budget should include support for the Principal Investigator and/or personnel based on annual percent effort. The IIS research agreement provides for reimbursement for travel related to presentation of study data at conferences/congresses so please do NOT include this as an expense.*