Study Protocol Cover Page

Official Study Title: Switching relapsing multiple sclerosis patients treated with natalizumab at risk for progressive multifocal leukoencephalopathy to teriflunomide: Is this safe and effective?

NCT#: NCT01970410

Note: IRB approval letter included and the February 25, 2015, date is the date the protocol was printed and saved. The document date and approval date is listed as February 24, 2015.

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Institutional Review Board

PROVIDENCE Health & Services

MEMORANDUM

Date: February 25, 2015

To: Stanley Cohan, MD, PhD
C/o: Katie Orwoll, Regulatory Associate, Providence Regional Research Office
From: Heather Murchison, Administrative Assistant, PH&S Institutional Review Board

Re: FULL-BOARD APPROVAL OF PROTOCOL MODIFICATION FOR:
(14-011B) Switching relapsing multiple sclerosis patients treated with natalizumab (Tysabri ®) at risk for progressive multifocal leukoencephalophy to teriflunomide (Aubagio®): Is this safe and effective? PI: Stanley Cohan, MD, PhD

This letter acknowledges the protocol modification notice concerning the following revisions to this study:

- Amended Protocol, tracked and clean versions.
- Addition of Drs. Ben Jacobson and Alan Morimoto, Removing Dr. John Roll

This report was approved at the full board meeting held on February 24, 2015.

CLINICAL TRIAL PROTOCOL

Compound: Teriflunomide

Title of Study:

Switching relapsing multiple sclerosis patients treated with natalizumab at risk for progressive multifocal leukoencephalopathy to teriflunomide: Is this safe and effective?

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1. **Introduction and rationale:**

Teriflunomide

Teriflunomide is the primary metabolite of leflunomide, [1] which is marketed worldwide for the treatment of rheumatoid arthritis. Teriflunomide inhibits dihydroorotate dehydrogenase (DHODH), the forth enzyme in the de novo synthesis pathway of pyrimidines. [2] Activated T-lymphocytes utilize both the de novo pyrimidine and salvage pathways of pyrimidines ribomicleotide synthesis. [3] After mitogen stimulation, teriflunomide inhibits in vitro T cell proliferation, DNA and RNA synthesis and expression of cell surface and nuclear antigens that are directly involved in T-cell activation and proliferation. [4]

Natalizumab (NTZ) is a FDA approved treatment for relapsing-forms of multiple sclerosis (MS) with pivotal studies showing an annualized relapse-rate (ARR) reduction of 68%, a reduction of new gadolinium (Gd+) lesions by 92% and a reduction of disability of 42% compared to placebo.[5] NTZ is highly effective in controlling MS but the risk of developing progressive multifocal leukoencephalopathy (PML) increases with the duration of the use of natalizumab. It can have a serious and life threatening complication in about 1 in 500 to 1 in 250 patients who have had more than 18 infusions and who have a detected antibody (Ab) for the JC virus. [6] The risk of PML is much greater in patients who have had prior immunosuppressive (IS) treatment. The combination of detected anti-JCV Ab , duration of NTZ treatment of greater than 24 months and prior IS increases the risk of developing PML to an incidence of 11 per 1000 treated patients. [7] There is a need to have an alternative MS disease modifying treatment (DMT) to use for patients at risk of developing PML from NTZ treatment that might be sufficiently effective so as not to have the patients' MS worsen while lowering or eliminating the risk of PML.

Many neurologists treating MS patients have not prescribed natalizumab due to a fear of PML developing in their patients. If an effective treatment alternative could be found for patients who have been treated with natalizumab for 12 months or longer and who test positive for the anti-JCV-Ab, perhaps more neurologists would use natalizumab earlier in the disease state for patients with unstable disease. Conversely, for patients with anti-JCV-Ab detected who have been treated with natalizumab for more than 12 months, many are continued on natalizumab due to fear that their MS might exacerbate off of the medication.

In a single center report of NTZ withdrawal in an attempt to lower the risk of PML, 32 patients who have received more than 12 months of NTZ were withdrawn from NTZ and not placed on any other disease modifying therapy (DMT). Eleven of the patients (38%) had at least moderate relapse of their MS and 2 had a severe relapse with an immune reconstitution inflammatory syndrome (IRIS) with multiple gadolinium enhancing (Gd+) lesions with edema. [8] Two of the patients who relapsed during the NTZ withdrawal had relapsed while receiving therapy. There was a higher rate of relapse in patients who were a bit younger (mean of 32.5 versus 40.6). In another reported observation series of NTZ withdrawal, patients who did receive an alternative DMT did have a much lower relapse rate and they were no cases of IRIS-like syndrome.[9]

In two controlled studies of NTZ withdrawal, approximately 1/3 of patients withdrawn from NTZ experienced either a clinical or MRI relapse or both regardless of post-NTZ treatment. Eighty-eight patients treated with NTZ for 24 months in Italy, who were anti-JCV-Ab positive were continued on NTZ, on another DMT or on no DMT. Those continued on NTZ experienced a

3.7% exacerbation rate over one year, those on another DMT experienced a 17.8% exacerbation rate and those on no DMT had a 16.7% exacerbation rate. [10] Teriflunomide was not one of the DMTs used in this study but it did not appear that the use of a DMT affected the exacerbation rate, although the initiation of the DMT used varied widely.

Another study followed 175 patients who had been treated with NTZ for 12 months or greater. Anti-JCV-Ab status was not considered. There was a 3 month interval between the last dose of NTZ and the initiation of a DMT which may have been IVMP, GA, IFN or placebo. The observed relapses clinically and/or of Gd+ recurrence was between 3 and 4 months and often proceeded by an elevation of alpha4-integrin saturation. [11] The focus of the report was that of PK, PD and MRI measurements rather than clinical status so that details of clinical status were not reported but there were several patients noted who had more than 10 acute Gd+ lesions with acute black holes indicating that, at least a few patients, had a hyperacute withdrawal from NTZ that was more severe than just a return to baseline MS activity prior to NTZ treatment.

In a treatment trial with IVMP after NTZ withdrawal, IVMP was found not to prevent return of MS disease activity or rebound activity. [12] Forty-three patients were given IVMP for 6 months after NTZ withdrawal on a monthly basis. Twenty patients (42%) had radiological or clinical disease activity above that seen in the pre-NTZ period and 9 patients (19%) had 'rebound' activity or 5 or more Gd+ lesions.

The use of fingolimod (FTY) to reduce recurrence of disease activity after NTZ discontinuation has been successful but it is highly correlated to when FTY is begun in relation to NTZ discontinuation. [13] Thirty-nine patients who switched to FTY after 24 weeks on NTZ were compared to 9 patients who became treatment free (TF). Nineteen (49%) patients in the FTY group compared to 7 (77%) patients in the TF groups experienced relapses after cessation of NTZ within 13 and 16 weeks. However, if FTY were begun in fewer than 12 weeks after FTY cessation, the ARR was reduced from 1.4 to 0.4. The percentage rate of relapse was not reported but it can be estimated, from the data, to be approximately 24% instead of 49% for those begun on fingolimod by 12 weeks after NTZ discontinuation. Earlier treatment initiation of fingolimod after NTZ discontinuation was not reported.

Another observation study did not show any benefit from any DMT after NTZ discontinuation.[14] From a total of 119 patients treated with NTZ, 36 stopped NTZ. At 1 year, the cumulative probability of relapse was 46% with the risk of relapse not modified by alternative therapy introduced after NTZ. "Despite the relative small size of our study and the various alternative therapies proposed, the association of methlyprednisolone with immunomodulator did not avoid the recurrence of the MS inflammatory activity, as attested by MRI Gd+ lesions and the occurrence of IRIS, responsible for EDSS increase." Teriflunomide was not among the options of DMT treatment, but half of the MS patients discontinued from NTZ returned to pre-NTZ treatment status or worsened, sometimes with an IRIS-like status similar to that reported by Dr. Kinkel. [15]

So in a review of the literature, including recent meetings, there is no consensus, and no data available to indicate what treatment could change the natural course of events to allow a significant relapse rate to occur after withdrawal from NTZ. It appears that early treatment with an effective and safe DMT may alter this poor prognosis of treatment withdrawal from NTZ. Teriflunomide may be that DMT.

With continued MRI and clinical vigilance, any PML patient should be identified rapidly and appropriate intervention begun. This is to be compared to the return of relapse rate or more

serious disease in a few months after NTZ discontinuation unless an effective and safe alternative can be identified.

Our own experience with transition from NTZ to teriflunomide is limited but so far favorable. Since the availability of teriflunomide in September, 2012 we have had a total of 15 patients who had been on NTZ over 24 months with anti-JVC-Ab positive status switch from NTZ to teriflunomide.. The mean number of days from the last NTZ infusion to the first dose of teriflunomide was 39 days. Of these 15 patients, one discontinued due to diarrhea after 20 days, but the other 14 had good tolerance Four of the patients have been on teriflunomide for fewer than 30 days at this time so that no meaningful comment of stability after NTZ withdrawal can yet be stated. The remaining 10 patients have been on teriflunomide for a mean of 87 days with five of this patients on teriflunomide more than 120 days. None of the patients experienced any recurrent or new MS symptoms and none have had an exacerbation at this time.

2. Study and Safety Objectives

A priori concept: that teriflunomide will be safe and effective to prevent relapses in patients with relapsing types of MS when switching from NTZ to teriflunomide in patients at risk for PML provided that the switch to teriflunomide from the last dose of NTZ is carried out in fewer than 4 weeks and provided that the patient has been clinically and radiologically stable during the NTZ treatment period.

2.1. Primary objective

Proportion of patients relapse free at 12 months

2.2 Secondary objectives

1) Time to return of radiological evidence of MS activity with new Gd+ lesions on cranial MRI.
2) EDSS sustained progression for 3 months as measured by at least 0.5 increase from baseline or 1 in any EDSS set score.
3) Number of new T2 or enlarging T2 hyperintensities on monthly sentinel brain MRIs

3. Study design

Patients with relapsing forms of MS, ages 21 to 60, male or female, not pregnant and not lactating and not planning to become pregnant during the study, who have had 12 or more continuous infusions of NTZ , who are anti-JCV-ab positive, and who had been free of clinical relapses during prior 12 months of NTZ therapy will be offered participation in this study. There will be limited wash-out period after discontinuation from natalizumab. It will be expected that each patient will be able to begin teriflunomide at 4 weeks (+/- 7 days)after last dose of NTZ based on formulary limitation. After informed consent is obtained screening measures will be completed including TB screening either with a PPD skin test or quantiferon gold for tuberculosis, a non blinded EDSS, 3T brain MRI, complete metabolic panel and CBC, and if female and potentially fertile, serum HCG will obtained.
The Becks depression scale will also be completed at this time.

Duration of the first phase of the trial will be six months . Liver function tests (LFTs) will be done per FDA guidelines, urine HCG for females of childbearing potential, contrast enhanced brain MRI, physical exam, neurologic exam and EDSS will be performed. Adverse Events (AE's)s will be recorded along with any change in concomitant medications. At subsequent clinic visits, Physical, EDSS and AE recordings will be at months 9, 12, 18 and 24. CBC and Metabolic panel laboratory evaluations at months 12,18, and 24, and MRI will be done at months 12 and 24. Symbol Digit (SDMT) will be administered at Baseline, months 6, 12 and 24.

There will be an interim analysis of data outcome and safety measures at 6 months, 12 months and 24 months.

After screening measures are completed and results reviewed, patients who qualify for the study will begin teriflunomide 14 mg daily within 4 weeks (+/- 7 days) of their last dose of NTZ. The first monthly brain MRI will be carefully reviewed and compared to baseline MRI to be sure there is no emergence of PML at that time.

3T brain MRI will be performed with standard MS protocol using Gadovist (gadobutrol) at a dose of 0.1 mL/kg (0.1 nmol/kg) with post-contrast administration to begin no sooner than 10 min after administration.

The three main readers who each will back up the other are Joseph Cousins PhD MD, Gaetano Pastena MD and James Thomas MD from the Albany (Latham) site using Siemens 3T Verio, or the GE 3T and Drs John Roll and Alan Morimoto from the Portland (OR) site using Philips Achieva 3.0T, to be done at Center for Medical Imaging-Tanasbourne. Dr. Thomas will be the overall reviewer for all MRIs. All scans will include the following:

1. 1mm 3d FLAIR T2 sequence with reformat 3mm sagittal and axial 3mm (Scans will be 3mm thick only)

32. Axial t1 pre contrast 3mm thick

3. Axial DWI

4. Axial t2 tse 3mm thickness

5. 3mm thick axial Spin Echo T1 post contrast.

Contrast agent: gadobutrol weight based single dose. 10 minute delay after injection and post contrast scan.

See flow sheet for study specific measures.

Adverse Events that are recorded during the trial and are considered to be study related and significant by the investigator, will be reported to the study sponsor and to Medwatch by the sponsor.

Study medication for this trial will be supplied through the subjects medical insurance. This trial does not have placebo element, therefore there will be no method of applying subjects to a treatment group.

Statistical Analyses:

In general, continuous variables will be presented with summary statistics (mean, standard deviation, median, range), and categorical variables will be presented with frequency distributions. All analyses will be conducted using 2-sided confidence intervals at the 0.05 significance level, unless otherwise stated.

Primary Analyses:

The proportion of patients relapse-free at Month 12 will be analyzed using Kaplan-Meier survival analysis methodology.

Secondary Analyses:

EDSS sustained progression for 3-month as measured by at least 0.5 or 1 (in any functional system (FS) score) point increase from baseline will be summarized. Time to return of radiological evidence of MS activity and ttime to EDSS sustained progression will be analyzed using Kaplan-Meier survival methods.

Number of new T2 or enlarging T2 hyperintensities on MRI will be summarized by visit.

AEs and SAEs will be summarized. Patients who discontinued treatment will be summarized as well.

4. **Approximate number of patients to be evaluated:** 60 completers with up to 70 to be enrolled if needed with an expectation of 80% completion rate.

5. **Study population**

5.1. Inclusion criteria:

1. Male and female patients, age 21 to 60 with relapsing forms of MS, treated with natalizumab for 12 consecutive months or longer with anti-JCV Ab positive during that time period.
2. Able to understand and sign Informed Consent Document.
3. Stable disease during treatment with natalizumab. No clinical relapses for at least 12 months.
4. Stable MRI on follow-up MRI scans for prior 12 months without evidence of new or enlarging T-2 hyperintensities or Gd+ lesions.
5. No evidence of significant cognitive limitation or psychiatric disorder.
6. EDSS of 1.0 to 6.0 inclusive.

5.2. Exclusion criteria

1. Any mental condition of such that patient is unable to understand the nature, scope and possible consequences of the study.
2. Patients that are known HIV positive.
3. Patients with a known history of hepatitis.
4. Known history of active tuberculosis not adequately treated, or a positive ppd skin test or positive quantiferon gold.
5. Any persistent or severe infection.
6. Any malignancy within 5 years, except for Basal or Squamous cell skin lesions, which have been surgically excised, with no evidence of metastatis.
7. Clinically relevant or unstable cardiovascular, neurological (i.e. progressive weakness, increasing hypesthesia), endocrine, or other major systemic diseases.
8. History of drug or alcohol abuse within the past year.
9. Any significant depression or psychiatric disease (BDI II greater than 25) within the past year.
10. Any significant lab abnormality as deemed by the investigator including but not limited to the following:
    a) Hypoproteinemia with serum albumin < 3.0g/dl.
    b) Serum creatinine >133umol/L (or >1.5 mg/dl)
    c) Hematocrit <24% and/or
    d) Absolute white blood cell count < 4,000 cells/mm3 (µl) and/or
    e) Platelet Count <150,000 cells/mm3 (µl) and /or
    f) Absolute neutrophil $\leq$ 1,500 cells/mm3 (µl)
    g) Liver function impairment or persisting elevations of SGPT/ALT, SGOT/AST, or direct bilirubin greater than 1.5 fold the upper limit of normal.
11. Any confounding illness or other diseases of the spine or bone that would impair evaluation of the patient or treatment effects.
12. Any clinical, CSF or MRI evidence for PML, from historical MRI review and results of screening MRI
13. Prior treatment with immunosuppressive drugs except for past use of intravenous steroids to treat MS relapses.
14. Pregnant or breast feeding women.
15. Women of childbearing potential not protected by effective contraceptive method of birth control and/or are unwilling or unable to be tested for pregnancy.

Known history of hypersensitivity to teriflunomide or leflunomide

16. Known history of hypersensitivity to teriflunomide or leflunomide.
17. Known history of chronic pancreatic disease or pancreatitis.
18. Prior use within 4 weeks before randomization of cholestyramine, or products containing St. John's Wort or concomitant use of Glatiramer acetate, interferons or any other FDA approved DMT due to potential confounding effects on efficacy results.

6. **Breakthrough disease**

1. Definition of relapse: a new objectively verified neurologic sign not associated with fever or infection, lasting at least 24 hours with an increase of one or more grade in two or more scales if the EDSS, or an increase of 2 or more grades in one functional scale. IF the patient has a baseline EDSS of 5.5 or 6.0, then an increase of 0.5 or greater in EDSS.
2. Treatment: if there is clinically appropriate need for treatment, then a standard dose of intravenous methyprednisolone (IVMP), usually 1000 mg for 3 consecutive days.

7. **Criteria to reduce reproductive risk**

Female subjects must not be breast feeding or pregnant (as confirmed by a serum pregnancy test) at the time of study entry and must agree to undergo urine pregnancy testing throughout the study. In addition a pregnancy test should be conducted in case of an unexpected delay of menorrhea.

For subjects of childbearing potential/child fathering potential, an adequate contraception method is required to prevent pregnancy during the course of the trial and while taking teriflunomide. The adequate contraception method is up to the Investigator's discretion. The contraception method must be clearly documented in the source documents. The importance of not fathering/bearing a child while using teriflunomide is to be communicated to the subject and is the responsibility of the treating Investigator. The subject is to be counseled by the Investigator on the importance of reporting to site staff a delayed onset of menses or if they have any suspect of pregnancy in themselves or female partner. If the subject is not of childbearing potential/child fathering potential or their partner is not of childbearing potential/child fathering potential, this must also be documented clearly in the source documents.

8. **Concomitant Treatments**

All treatments being taken by the patients on entry to the study or at any time during the study are regarded as concomitant treatments and should be documented. A history of previous treatments for MS should be documented for the prior 2 years,

Medications that are permitted during the study may be used as clinically indicated at the physician's discretion. However, medication with a low therapeutic index such as digoxin should be carefully monitored. All efforts should be made to adhere to the same dosing regimen during the conduct of the trial. The combined use of teriflunomide and nonsteriodal anti-inflammatory drugs (NSAIDS) may be associated with an increased incidence of hypertension. Blood pressure (BP) must be monitored carefully before treatment and at regular visits during study medication administration.

The following concomitant treatments or any prior use of these treatments are not permitted due to potential effects on the immune system:

- Cladribine or mitoxantrone
- Azathioprine, cyclophosphamide, cyclosporine, methotrexate, or mycophenylate
- Leflunomide and any prior use of teriflunomide.

The following treatments are not permitted during the study and prior to entry into the study For durations noted, due to potential pharmacokinetic or pharmacodynamic interactions with The study medication:

- St. Johns Wort products containing hyperforin in an unknown percentage or greater than 1% of the extract. High amounts of hyperformin in St Johns Wort extract has been shown to induce CYP3A4 enzymes and potentially increase ethyl estradiol and norethindrone clearance.
- Cholestyramine or activated charcoal, which results in the accelerated elimination of teriflunomide
- Glatiramer acetate, interferons or any other FDA approved DMT due to potential confounding effects on efficacy results.

9. **Adverse Events**

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

In the event that a subject is withdrawn from the study because of an adverse event, it must be recorded on the CRF as such. The subject should be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized.

Serious Adverse Events

A serious Adverse Event (SAE) means any adverse event fitting the description above but also containing one of the following:

- Death
- Life threatening experience which places the subject at immediate risk of death from the event as it occurred.
- Full Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect

Any reports of these events during the conduct of the study will immediately be reported to the sponsor, and the IRB within 5 days of the investigator learning of it . The sponsor will alert the FDA and submit to Medwatch. The Medwatch FDA Form 3500 should be used when submitting an SAE.

Discontinuation of Study Treatment

1. If the patient becomes pregnant (accelerated withdrawal protocol to be used)
2. at the discretion of the Investigator for medical or ethical reasons.
3. If the patient withdraws consent
4. If the patient is unwilling or unable to comply with the protocol

Any patient discontinuing teriflunomide may be treated with an 11day course of cholestyramine or activated charcoal according to standard use protocol if indicated.

Data Safety Monitoring Board (DSMB)

A DSMB will be established consisting of 3 respected scientists, not involved with the study or with Genzyme, to periodically review developing outcomes and safety data. The DSMB is an independent, paid committee with dual responsibility for the overall safety of the participants and integrity of the study. The DSMB can make recommendations to discontinue the study permanently or to place the study on hold to determine if the study is safe to continue. The DSMB will provide a written summary of their periodic reviews and recommendations' which will then be forwarded by each investigator to their Investigational Review Board (IRB)

There will be an interim analysis of data outcome and safety measures at 6 months to include the first 20 patients completing the month 6 visit, and subsequently at 12 months and 24 months.

10. **Expanded Disability Status Scale (EDSS)**

Based on a standard Neurological Examination, the 7 functional systems are rated per standard format. [16] The EDSS are administered in person by the treating neurologist and is not a blinded exam

11. **Becks Depression**

The Beck Depression Inventory-II (BDI-II) is a multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression. [17]

12. **Symbol Digit Modality Test (SDMT)**

The symbol digit modality test is brief and easy to administer and has demonstrated remarkable sensitivity in detecting not only the presence of brain damage but also changes in cognitive functioning over time and in response to treatment.

Enrollment, end of study Publication/presentation plans

a) submission of draft proposal, budget and payment schedule to Sanofi by Dr. Edwards and MS Center staff by Friday, May 31 2013
b) enrollment of first patient begins one month after contract received by MS Center of NE New York with 5-10 patient enrolled monthly.
c) no more than 30 days expected for IRB approval and study start up ready
d) date of first patient to first 10 patients likely to be 4 weeks after contract received and approved.
e) end of 30 patient enrollment approx Sep 31, 2014

Submission to a national and/or international meeting as soon as the data have been analyzed, most likely ECTRIMS 2014 and possibly CMSC 2014, AAN 2014, ENS 2014. Submission to a peer review journal within 6 months of study analysis completion (*Neurology* or *MSJ*).

13. Source Documentation and Case Report Form Completion

Source documents are defined as original documents, data and records. These may include hospital records, clinical and office charts, lab results, cognitive data and information, etc. The Case Report Form documents will serve as the source records for this trial. All forms will be completed within 5 business days of the study visit. A CRF will be provided for each enrolled study subject. All CRFs will be completed using black ink. All corrections will be made by striking through with a single line and writing correct data above, beside, or below the erroneous data, so as not to obscure the original entry. Each correction will be initialed and dated by the person making the correction.

Dr. Edwards' site will create the CRFs, monitor data and submit data to Dr. Ma for statistical analyses. Dr. Cohan's site will prepare the ICF. Dr. Cohan's site will provide study data to Dr. Edwards's site. (fax: 518-785-5000 or by pdf: kedwards@tristateneuro.com and cgorman@tristateneuro.com Study data includes any AE's.

14. Retention and Availability of Records

The investigator will maintain adequate records for the protocol including signed Informed consents, patient information sheets, completed source documents, CRF's, Lab reports, Medical records, AE reports and information regarding all subjects who discontinued.

15. Ethics

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigators Brochure if applicable, informed consent/assent, and all other forms of subject information related to the study (including advertisements) be reviewed by the IEC/IRB. IRB approval is mandatory before initiating of any study related activities.
The study will be conducted per the protocol, in accordance with ICH guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

16. **Use of Information/Confidentiality**

All information obtained during the conduct of this clinical trial is considered confidential. This information may be disclosed as deemed necessary by t the MS Center of Northeastern New York (MSCNENY) or Genzyme to other clinical investigators, the IEC/IRB, the FDA and other governmental agencies. Patient identifiers will include patient assigned number, age, and sex. Patient Initials will not be released to the company as this is irrelevant information. The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study by name and subject number. This list will be maintained at the investigative site.

17. IND Safety Reporting: Sponsor will provide 3 copies of safety reports to MSCNENY for distribution to Dr Cohen's site and the IRB

18. References

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Schedule of Events

Procedure/Visit		Screen	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 18	Month 24/ET	UNS Relapse
ICF		x												
Med History		x												
MS History		x												
Inc/exc		x	x											
Vitals		x	x	x	x	x	x	x	x	x	x	x	x	x
PE		x	x	x	x	x	x	x	x	x	x	x	x	x
EDSS		x	x	x	x	x	x	x	x	x	x	x	x	x
Becks		X							x		x		x	
SDMT			x						x		x		x	
Metabolic panel		x							x		x		x	
CBC (a)		x							x		x		x	
LFTs (b)			x	x	x	x	x	x						
Serum preg * Urine preg		*	x	x	x	x	x	x	x	x	x	x	x	
PPD or QG		x												
MRI		x		x	x	x	x	x	x		x		x	x
Con meds		x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events			x	x	x	x	x	x	x	x	x	x	x	x

(a) CBC will include WBC (Count), RBC (Count), Hemoglobin, Hematocrit, Mean Corpuscular Hemoglobin (MCH), Platelet (Count, Neutrophils, Monocytes, Lymphocytes, Eosinophils, Basophils

(b) LFT's will be SGGT, Bilirubin, Total; Bilirubin, Direct; Bilirubin, Indirect; Alkaline Phosphatase Transferase, aspartate amino (AST) (SGOT); Transferase, alanine amino (ALT) (SGPT).

****Window for Screen to Baseline visit is 21 to 35 days.
****Window on all other visits is plus or minus 7 days