A Randomized, Controlled, Open-Label Study to Evaluate the Efficacy of Extracorporeal Photopheresis (ECP) versus Corticosteroids in the Treatment of Patients with Secondary Progressive Multiple Sclerosis (SPMS)

Sponsor:	**Daniel R Couriel, MD**. Director Adult BMT Program and ECP Division of Hematology/Oncology University of Michigan, Ann Arbor, MI
Clinical Monitor:	University of Michigan Institue of Clinical and Health Research (MICHR)
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IDE No.:	G140079
Study Device and Drug Name:	THERAKOS® CELLEX® Photopheresis Systems
Development Phase:	Investigator Initiated Protocol
Protocol Version and date:	Version 3.0 July 24, 2015

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

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SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Randomized, Controlled, Open-Label Study to Evaluate the Efficacy of Extracorporeal Photopheresis (ECP) versus Corticosteroids in the Treatment of Patients with Secondary Progressive Multiple Sclerosis (SPMS)

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1996, and the guidelines on Good Clinical Practice.

_____ _____

Daniel R Couriel, MD
Director, Adult BMT Program and ECP
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Date

Declaration of the Principal Co-Principal Investigator

Title: A Randomized, Controlled, Open-Label Study to Evaluate the Efficacy of Extracorporeal Photopheresis (ECP) versus Corticosteroids in the Treatment of Patients with Secondary Progressive Multiple Sclerosis (SPMS)

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PROTOCOL SYNOPSIS

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Title	A Randomized, Controlled, Open-Label Study to Evaluate the Efficacy of Extracorporeal Photopheresis (ECP) versus Corticosteroids in the Treatment of Patients with Secondary Progressive Multiple Sclerosis (SPMS)
Study Duration	2 years
Study Center	University of Michigan (Single Center)
Objectives	**Primary objective:** To evaluate the effect of ECP compared to pulsed corticosteroids on accumulation of disability at 12 months (i.e. 52 weeks, see below Section 9.1 for schedule) in individuals with secondary progressive multiple sclerosis (SPMS). Disability will be assessed using a composite measure that takes into account changes in the Expanded Disability Status Scale (EDSS) score and components of the Multiple Sclerosis Functional Composite (MSFC) score. **Secondary Objectives:** • To assess the effect of ECP versus corticosteroids on plasma levels of immunological factors and the frequency of circulating myelin-reactive Th1 and Th17 cells • To determine whether changes in immunological parameters that occur following initiation of ECP or corticosteroids correlate with clinical outcomes • To assess the impact of ECP versus corticosteroids on EDSS scores every 3 month time point through 2 years compared to baseline • To assess the impact of ECP versus corticosteroids on MSFC three dimensional composite z-score at every 3 month time point through 2 years compared

	to baseline • To assess the effect of ECP on risk of clinical relapse • To assess the effect of ECP versus corticosteroids on the frequency of gadolinium- enhancing T1 weighted lesions on cranial MRI scans obtained at months 6 and 12 compared to baseline • To assess the effect of ECP versus corticosteroids on interval changes in T2 weighted lesion number and volume at months 6 and 12 compared to baseline. • To assess the tolerability and the safety profiles of ECP versus corticosteroids
Number of Subjects	N=66 subjects (33 per treatment arm)
Study design	This is a Phase II, open-label, randomized, study of ECP versus pulsed corticosteroids in patients with SPMS. Subjects will be randomized at a 1:1 ratio to receive ECP (study arm) or active treatment with intravenous methylprednisolone pulses (control arm) administered every 4 weeks (1 gram per infusion) for 12 months. All subjects will undergo longitudinal MSFC and EDSS testing at baseline and every 3 months through 2 years (See Section 9.1 for timing of schedule of assessments)). Blood will be collected for immunological testing at baseline, months 3, 6, 9 and 12. Subjects will also undergo neuroimaging with brain MRI at baseline and months 6 and 12 following initiation of treatment
Study endpoints	**Primary:** Proportion of subjects with no evidence of disease progression at 2 years, defined as a minimum change from baseline in one or more of the following: • 20% or greater increase in the timed 25 foot walk • 20% or greater increase in the 9 hole peg test • 1 point or greater increase in EDSS score in subjects with baseline EDSS scores between 3 and 5.5 • 0.5 point or greater increase in EDSS score in subjects with baseline EDSS scores equal to or greater than 6 **Secondary**:(1) change in plasma levels of immunological factors and frequencies of IFNγ and IL-17 MBP-specific PBMC at months 3, 6, 9 and 12 compared with baseline; (2) adverse events; (3) MSFC 3 dimensional composite z-score every 3 months through 2 years compared to baseline;

	(4) EDSS score every 3 months through 2 years comparedto baseline; (5) percentage of subjects with improvement (as defined for the primary endpoint) at months 6 and 12; (6) occurrence of clinical relapse at any point in the study; (7) interval change in T2 lesion number and volume on MRI scans obtained at months 6 and 12 compared to baseline; (8) the number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12; (9) interval change in the number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12 compared to baseline.

Patient Population	**Inclusion Criteria**	Subjects will be entered into this study only if they meet the all of the following criteria: 1. Patients with SPMS based on the Recommended Diagnostic Criteria for MS and clinical course. Secondary progression is defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses. 2. Demonstrate EDSS scores between 3 to 6.5 at screening. 3. Documented EDSS progression in the 2 years prior to screening of 1 point or greater for patients with an EDSS score less than 6 at baseline, and greater than or equal to 0.5 for patients with an EDSS score greater than or equal to 6.0 at baseline. If documented EDSS scores are not available, a written summary of the clinical evidence of disability progression over the last 2 years, and retrospective assessment of EDSS score from data in the medical records, must be submitted for review by the principal investigators. 4. Documented absence of clinical relapse within 2 years of screening 5. Age ≥ 18 ≤ 75 years 6. Weight > 40 kg. 7. Absolute Neutrophil count ≥ 2,000 per μL 8. Hematocrit ≥ 28 % and platelet count > 100,000 per μL (with or without transfusion support) 9. Willingness to use at least 1 reliable method of birth control (e.g. abstinence, oral contraceptives, intrauterine devices, barrier method with spermicide, or surgical sterilization) throughout the study for all men and women of childbearing potential 10. Willingness to participate in all study visits and procedures, as outlined in the informed consent 11. Patients able to give informed consent.

	Exclusion Criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study: 1) Absolute medical contraindication to corticosteroid treatment 2) Absolute medical contraindication to receive ECP 3) Clinical relapse within 2 years of screening 4) Laboratory evidence of any of the following: a) WBC < 2,000 cells per uL b) Serum transaminase levels > x 2 UNL c) Creatinine Clearance < 60 mL/min d) HgbA1C > 6% 5) Concurrent diagnosis of a neurological condition that would interfere with the assessment of MS, or an autoimmune disease or inflammatory condition that is chronically treated with immunosuppressive agents, including systemic corticosteroids. 6) Evidence of known infection with human immunodeficiency virus (HIV) or active (not including latent) Hepatitis B (laboratory testing is not required if virus status is already known) 7) Uncontrolled infection requiring treatment at study entry 8) Hypersensitivity or allergy to psoralen (methoxasalen) 9) Hypersensitivity or allergy to both heparin and citrate products (If hypersensitive or allergic to only one of these products, exclusion does not apply) 10) Inability to tolerate fluid changes associated with ECP (e.g. inadequate renal, hepatic, pulmonary and cardiac function leading to enable patient to tolerate extracorporeal volume shifts associated with ECP) 11) Presence of aphakia or photosensitive disease (systemic lupus erythematosis, porphyrias, albinism, etc.) 12) Women who are pregnant and/or lactating. 13) Use of any investigational drug/treatment at the time of enrollment or within the previous 60 days, or five elimination half-lives, or until the expected pharmodynamic effect has returned to baseline, whichever is longer. 14) Initiation of dalfampridine or change in the dose of dalfampridine within 6 months prior to randomization

	Exclusion Criteria	15. Treatment with any of the medications or procedures listed below: a) Glatiramer acetate, interferon-beta, fingolimod, teriflunomide or dimethylfumarate within 3 months prior to randomization b) Natalizumab within 3 months prior to randomization c) Cyclophosphamide within 1year prior to randomization d) Mitoxantrone within 1 years prior to randomization e) Rituximab, within 6 months prior to randomization f) Ofatumumab, ocrelizumab, cladribine, daclizumab within 2 years prior to randomization g) Intravenous immunoglobulin within 6 months prior to randomization h) Plasmapheresis within 6 months prior to randomization 16) Corticosteroids within 3 months prior to screening, with the following exceptions: Topical ointments or creams, or eye drops that contain corticosteroids; Intranasal Steroids or Oral Steroids given in a single dose as a premedication for a procedure such as gadolinium-enhanced MRI. 17) Inability to undergo MRI scans. Contraindication to gadolinium due to past allergic, hypersensitive or adverse reaction or impaired renal function. Patients receiving a steroid prep prior to Gadolinium administration due to history of hypersensitivity or allergy to other agents or due to prior mild reaction to Gadolinium will not be excluded from the study. 18) Any other disease or condition which, in the opinion of the investigator, could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with study procedures. 19) Poor venous access 20) Previous history of skin cancer, leukemia/lymphoma/myeloma or bone marrow transplant. 21) Patients taking Coumadin who are unable to switch from oral anticoagulants to enoxaparin.

		22. Heparin-induced thrombocytopenia 23. Poor cardiac function 24. Severe hypotension

Study treatment	Study Arm: ECP, Control Arm: Pulsed corticosteroids
Dosage and frequency of administration	Study Arm: Weeks 1-8: 3 times per week Weeks 9-16: Twice per week Weeks 17-36: Treatment on two consecutive days every 2 weeks (or optionally, one treatment per week) Weeks 37-44: Once every 2 weeks Weeks 45-52: Once every 4 Weeks Control Arm: Pulsed corticosteroids (1 gm. of MP IV every month) for 52 Weeks.
Duration of Administration	1 year (52 weeks)
Statistical methods	An intent to treat approach will be used. The proportion of subjects who show no evidence of disease progression, as defined above, will be compared between treatment groups using the Chi-square test. Two-sample t-tests or Wilcoxon rank sum tests will be used to assess treatment differences in continuous outcomes and chi-square or Fisher's exact tests will be used for categorical outcomes.
Power and Sample Size	Assuming that the proportion of subjects in the corticosteroid treatment who show no evidence of disease progression at Week 52 is 30%, 66 subjects (33 per treatment arm) provides at least 80% power to detect a treatment difference of 30% (i.e., 60% of the ECP treated subjects will improve at Week 17), based on the normal approximation of the binomial distribution and a one-sided Type I error of 5%.

LIST OF STUDY PERSONNEL

Sponsors	**Daniel R Couriel, MD. Director Adult BMT Program and ECP. University of Michigan**
Principal Investigator	**Daniel R Couriel, MD.** **Director Adult BMT Program and ECP.** **University of Michigan** dcouriel@umich.edu. Tel 734-936-8785
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Laboratory	University of Michigan Clinical Laboratories for routine studies Neuroimmunology Laboratory, Dept. of Neurology for research studies (Dr. Segal, Director)

TABLE OF CONTENTS

Tables in Text

Figures in Text

List of Appendices

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase (previously known as serum glutamic pyruvic transaminase, SGPT)
AST	Aspartate aminotransferase (previously known as serum glutamic oxaloacetic transaminase, SGOT)
BBB	Blood Brain Barrier
CI	Confidence interval
CNS	Central Nervous System
CRF	Case report form
CS	Corticosteroids
CTCL	Cutaneous T-cell lymphoma
DMA	Disease Modifying Agents
DRL	Drug Reference List
ECP	Extracorporeal Photopheresis
EDSS	Expanded Disability Status Scale
eCRF	Electronic case report form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GVHD	Graft vs. Host Disease
HIV	Human immunodeficiency virus
9-HPT	9-Hole Peg Test
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary of regulatory activities
MP	Methylprednisolone
MS	Multiple Sclerosis
MSFCS	Multiple Sclerosis Functional Composite
PASAT	Paced Auditory Serial Addition Test
PPMS	Primary Progressive Multiple Sclerosis
QoL	Quality of Life

RRMS	Remitting Relapsing Multiple Sclerosis
SAE	Serious adverse event
SD	Standard deviation
SPMS	Secondary Progressive Multiple Sclerosis
SUSAR	Suspected unexpected serious adverse reaction
UNL	Upper Limits of Normal
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet Wave Length A
WHO	World Health Organization

1. INTRODUCTION

1.1 Background

Multiple Sclerosis

Multiple Sclerosis (MS) is chronic inflammatory disease affecting the central nervous system (CNS). MS is the most common cause of non-traumatic neurological disability among young adults in the Western Hemisphere. It affects over 400,000 individuals in the United States alone, approximately 2.5 million people worldwide, and its incidence is on the rise. The symptoms of MS are protean, reflecting the multifocal nature of the disease. They include visual loss, spastic paraparesis, numbness, urinary incontinence, gait imbalance, fatigue, double vision, tremor and cognitive impairment.

In the majority of cases, MS initially follows a relapsing-remitting (RRMS) course characterized by discrete episodes of neurological symptoms separated by clinically quiescent periods. Peripheral blood leukocytes cross the blood-brain-barrier (BBB) and infiltrate the brain, spinal cord and optic nerves to drive parenchymal lesion formation. Clinical exacerbation correlates with the development of lesions in "eloquent" areas. Natural history studies have shown that the incidence of relapses and breaches in the BBB decrease with disease duration (Filippi et al., 1997). However, the majority of individuals with RRMS ultimately enter a secondary progressive (SP) stage, characterized by the gradual accumulation of neurological disability. The molecular and cellular basis for this transition is unclear, and the role of inflammation during the SP stage is a subject of active debate. In fact, immunomodulatory disease modifying agents (DMA) that are used to manage RRMS tend to lose efficacy following transition to a SPMS stage (Panitch et al., 2004, Paolillo et al., 1999). Such observations have led to the proposal that the gradual accumulation of disability in SPMS is driven by neurodegeneration, manifested as neuronal cell death, Wallerian degeneration and astrogliosis, independent of the autoimmune assault that predominates earlier in the disease course (Trapp and Nave, 2008).

Conversely, a substantial body of data indicates that autoimmune inflammation is still relevant, and contributes to CNS tissue damage, during the SP stage. Others and we have found increased frequencies of circulating Th1 and Th17 cells in individuals with SPMS as well as RRMS (unpublished data). Neuropathological studies demonstrate widespread microglial activation and diffuse lymphocyte infiltration in the cerebral white matter of individuals with SPMS, as opposed to the lymphocyte-rich perivascular infiltrates that are characteristic of the RR stage (Frischer et al. 2009; Kutzelnigg. et al. 2005). Serafini and colleagues discovered lymphoid follicles in the sulci of brain specimens from patients with SP, but not RR, MS (Serafini et al., 2004). Hence, the nature of the aberrant immune response appears to evolve over the disease course, possibly explaining why the efficacy of individual disease modifying agents differs between the RR and SP phases. Mitoxantrone is the only therapy approved for the treatment of SPMS in the United States. However, the efficacy of mitoxantrone in SPMS patients without superimposed relapses is unknown and the considerably toxicities associated with this chemotherapy (including risk of leukemia and cardiomyopathy) limit its use. Therefore there is a considerable need for the development of new therapies that will slow or arrest disability progression in progressive MS without imposing considerable health risks.

Extracorporeal Photopheresis

ECP has been used clinically for nearly 20 years as an FDA-approved therapy for the palliative treatment of cutaneous T-cell Lymphoma (CTCL). This therapy is an apheresis-based process whereby autologous leukocytes are treated with a photoactivatable compound, 8-methyoxypsoralen, followed by exposure to ~1.5 J/cm^2 of UVA light and reinfused. This occurs in a point-of-care, patient-connected, sterile, closed-loop system. ECP has been applied for treatment to a wide variety of immunologic conditions, with minimal side effects.

UVADEX® (methoxsalen) Sterile Solution is a liquid methoxsalen (8-methyoxypsoralen) for *ex vivo* use in ECP therapy. It was developed to introduce methoxsalen as a liquid into the buffy coat bag during the ECP collection process followed by exposure of the cells to UVA light. In ECP therapy, when cells have absorbed the drug and are exposed to UVA radiation, covalent crosslinks between pyrimidine bases form within the deoxyribonucleic acid helix, preventing replication and leading to apoptotic cell death. Non-nucleated blood components, such as red blood cells, are not affected. At the end of the photoactivation cycle, the photoactivated cells are then reinfused back to the patient.

ECP has been used for treatment of SPMS in one small, pilot, controlled study (Rostami et al1999) and in several uncontrolled (Poehlau et al.,1997, Besnier et al., 2002) studies with inconclusive results. The heterogeneity of schedules and the short duration of therapy in these publications further complicate interpretation of the results.

At our center, 3 patients with documented SPMS were treated with ECP, following the procedures described in this protocol (Unpublished data). Two of these patients with SPMS treated with an intensive ECP regimen have shown objective improvements at 4 months; these improvements have persisted even after the treatments were tapered. At 4 months, the first patient no longer needed assistance to walk, and had significant improvement in all 3 components of the MSFC as follows: 53% in 25-foot walk, 67% in 9-hole peg test (9-HPT) and 17% in PASAT cognitive test. The second patient required a walker at the beginning of therapy, and at 4 months started ambulating comfortably with a cane. This patient maintained his 25-foot walk score, and had a 64% improvement in the 9-HPT and 20% in the PASAT cognitive test.

The Multiple Sclerosis Functional Composite (MSFC), see also Appendix 1

In this study, the MSFC scores (See Section 8.1.1) will be used as a primary outcome measurement. (Fischer et al., 2001) The MSFC is a validated composite measure developed by the National MS Society's Clinical Outcomes Assessment Task Force. The composite consists of the following components: a timed 25-foot walk (T25FW) test to measure leg function and ambulation; the timed nine-hole peg test (9HPT) to measure upper extremity dexterity and function; and the 3-second version of the paced auditory serial addition test-3 (PASAT), to measure neuropsychological function. Each component score is converted to a z-score by normalizing to a reference population. This instrument was designed in such a way that a single trained technician can administer this scale for consistency.

The Expanded Disability Status Scale (EDSS), see also Appendix 1

In addition, EDSS score (See Section 8.1.2) will be measured. Based on a standard neurological examination, the EDSS is a composite score that is commonly used to quantify disability level in patients with MS (Kurtzke et al, 1983). The composite is derived from ratings of 7 functional systems commonly affected in MS: visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral function. Higher scores indicate higher disability. Scores of less than 6.0 indicate independent ambulation, without the need for an assistive device such as a cane, walker, or wheelchair. The EDSS has become the standard disability score used in all of the recent product development trials.

Magnetic Resonance Imaging (MRI)

Longitudinal MRI studies have shown that the majority of MS lesions are asymptomatic. MRI is a sensitive tool for monitoring disease activity and for revealing asymptomatic dissemination of lesions in space and time. The pattern and evolution of MRI lesions can be highly suggestive of MS, and imaging studies are often an important component of the diagnostic work-up of demyelinating disease. (Traboulsee et al., 2006). Interval changes in the number and volume of T2 weighted lesions and the frequency of gadolinium enhanced T1 weighted lesions (indicative of new lesion formation) are often used as outcome measures in clinical trials of therapeutic agents in relapsing MS.

Corticosteroid Administration: Intravenous methylprednisolone (IVMP)

Pulsed intravenous corticosteroid therapy, in the form of IVMP at a dose of 1 g monthly for 1 year, was chosen as an active comparator for the control arm. Corticosteroid pulses are widely used in clinical practice to improve energy and motor stamina in individuals with progressive MS . They have a favorable side effect profile. This treatment has not been rigorously tested in placebo-controlled, double-blind Phase 3 clinical trials. However, a randomized, controlled, single blind phase 2 clinical trial of regular pulses of IVMP administered to MS patients over 5 years showed beneficial effects including prevention or delay of whole brain atrophy and disability progression, and suppression of T1-weighted MRI lesion formation (Zivodinov et al., 2001)

The present study is designed to assess the safety and efficacy of ECP therapy compared with pulsed corticosteroids in patients with documented SPMS.

1.2 Rationale

Great strides have been made in the development of drugs that are therapeutically beneficial in RRMS, resulting in the introduction of 10 DMAs approved by the Food and Drug Administration (FDA) for clinical use. In contrast, the treatment of SPMS remains suboptimal. The only FDA sanctioned drug for the management of progressive MS is mitoxantrone, a chemotherapeutic agent that is modestly effective and carries significant toxicities, including cardiomyopathy and leukemia. There is a dire need for novel agents that stabilize the disease course in patients with SPMS without imposing undue risks.

Although focal blood-brain-barrier breakdown and perivascular infiltrates are relatively more common in RRMS, a substantial body of data indicates that autoimmune inflammation is still relevant, and contributes to CNS tissue damage, during the SP stage. However, neuropathological studies indicate that the nature of the aberrant immune response evolves over the disease course and might explain why the efficacy of DMAs differs between the RR and SP phases. Our anecdotal experience at the UM suggests that ECP might be effective in the treatment of SPMS when administered using a more frequent and prolonged schedule than that used in previous studies. Based on this, and its favorable safety profile (both in MS and other conditions), we believe that a more rigorous evaluation of our protocol in SPMS is warranted.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of ECP compared to IVMP on accumulation of disability at 1 year (52 weeks) in individuals with secondary progressive multiple sclerosis (SPMS). Disability will be assessed using a composite measure that takes into account changes in the EDSS and components of the MSFC score.

2.2 Secondary Objectives

- To assess the effect of ECP versus corticosteroids on plasma levels of immunological factors and the frequency of circulating myelin-reactive Th1 and Th17 cells
- To determine whether changes in immunological parameters that occur following initiation of ECP or corticosteroids correlate with clinical outcomes
- To assess the impact of ECP versus corticosteroids on Expanded Disability Status Scale (EDSS) scores every 3 months through 2 years compared to baseline
- To assess the impact of ECP versus corticosteroids on MSFC three dimensional composite z-score every 3 months through 2 years compared to baseline
- To assess the effect of ECP on risk of clinical relapse
- To assess the effect of ECP versus corticosteroids on the frequency of gadolinium-enhancing T1 weighted lesions on cranial MRI scans obtained at months 6 and 12 compared to baseline
- To assess the effect of ECP versus corticosteroids on interval changes in T2 weighted lesion number and volume at months 6 and 12 compared to baseline.
- To assess the tolerability and the safety profiles of ECP versus corticosteroids

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a Phase II randomized, open-label study to evaluate the efficacy of extracorporeal photopheresis (ECP) versus IVMP on disability progression in subjects with SPMS. At the initial screening visit, an extensive medical history will be obtained and a detailed neurological examination will be performed to determine eligibility. Subjects who meet eligibility criteria will be enrolled in one of two study arms. Subjects will be randomized at a 1:1 ratio to receive ECP (study arm) or active treatment with intravenous methylprednisolone pulses (control arm) administered every 4 Weeks (1 gram per infusion) for 52 weeks.

ECP will be administered according to the following schedule:

Study Arm: Weeks 1-8: 3 times per week

Weeks 9-16: Twice per week

Weeks 17-36: Treatment on two consecutive days every 2 weeks (or optionally, one treatment per week)

Weeks 37-43: Once every 2 weeks

Weeks 44-52: Once every 4 Weeks

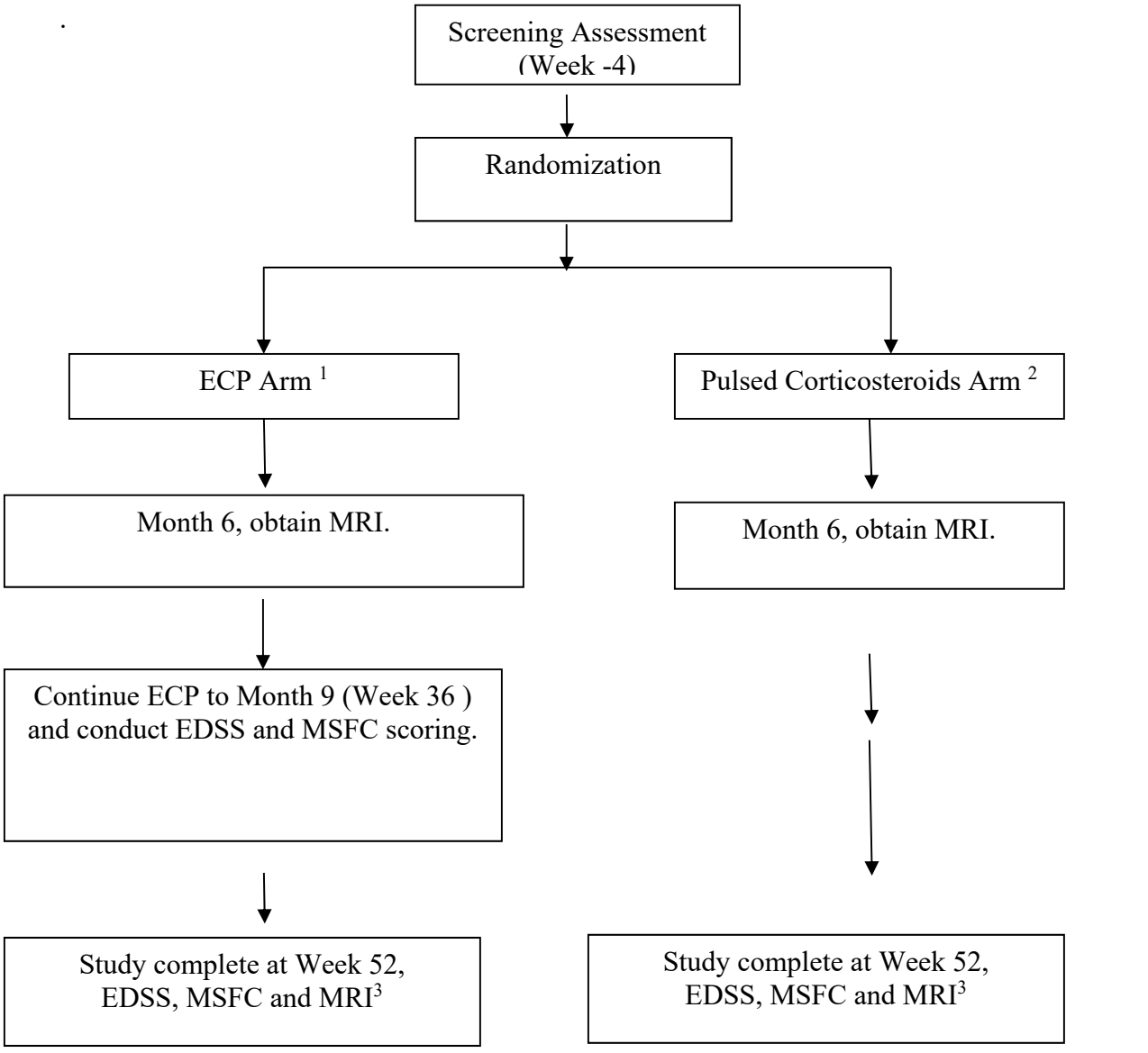
All subjects, including patients who receive corticosteroids, will be evaluated using the MSFC tool at baseline and every 3 months through 2 years (See Section 9.1 for timing of the schedule of assessments). They will also be scored using the EDSS at baseline and every 3 months through 2 years. Subjects in the control arm will be evaluated by MSFC and EDSS during the week prior to their next intravenous methylprednisolone infusion. Blood will be collected for immune function (cytokines) testing at baseline, and months 3, 6, 9 and 12. MRI will be done at baseline as well as months 6 and 12 following initiation of treatment; if the disability measurements are stable or improved at any point in time, then ECP will be continued per protocol..

Patients in the ECP arm should have all of their treatments with the CELLEX ® System. Patients randomized to the ECP arm must receive their treatment within 5 days of baseline visit.

In the ECP process, UVADEX ® (methoxsalen) Sterile Solution will be injected directly the recirculation bag of the extracorporeal circuit after completion of the buffy coat collection. The dose of UVADEX® (methoxsalen) Sterile Solution will be calculated based on the standard treatment volume formula (See Section 6.2).

For the schedule of assessments, please refer to Section 0.

Figure 1: Study Design



ECP=Extracorporeal Photopheresis MRI: Magnetic Resonance Imaging

[1] Frequency of ECP treatments:

Three times weekly for weeks 1-8, followed by a taper to twice weekly for weeks 9-16 and then twice consecutively every 2 weeks (or alternatively once weekly) for weeks 17-36, then once every 2 weeks for weeks 37-43, and once every 4 weeks for weeks 44-52.

[2] Pulsed corticosteroids, IVMP (1 g IV methylprednisolone) every 4 Weeks for 52 Weeks.

3 EDSS and MSFC will be assessed every 3 months through 2 years

3.2 Endpoints

3.2.1 Primary Endpoint

Proportion of subjects with no evidence of disease progression at week 52. Progression is defined as a minimum change from baseline in one or more of the following parameters:

- 20% or greater increase in the timed 25 foot walk
- 20% or greater increase in the 9 hole peg test
- 1 point or greater increase in EDSS score in subjects with baseline EDSS scores between 3 and 5.5
- 0.5 point or greater increase in EDSS score in subjects with baseline EDSS scores equal to or greater than 6

3.2.2 Secondary Endpoints

- Change in Plasma levels of Immunological Factors and Frequencies of IFNγ and IL-17 MBP-specific PBMC at Months 3, 6, 9 and 12 compared with baseline
- MSFC 3 dimensional composite z-score every 3 months through 2 years compared to baseline
- EDSS score every 3 months through 2 years compared to baseline
- Percentage of subjects with improvement (as defined for the primary endpoint) at Months 3, 6, 9 and 12 compared to baseline
- Occurrence of clinical relapse at any point in the study
- Interval change in T2 lesion number and volume on MRI scans obtained at months 6 and 12 compared to baseline
- The number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12 compared to baseline
- Interval change in the number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12 compared to baseline.
- Toxicity and Adverse events in both arms

3.3 Justification of the Study Design

Mitoxantrone is the only therapy FDA-approved for the treatment of SPMS in the United States. However, the efficacy of mitoxantrone in SPMS patients without superimposed relapses is unknown and the considerably toxicities associated with this chemotherapy (including nausea, alopecia, menstrual disorders, urinary tract infections, amenorrhea and SAEs such as secondary acute myelogenous leukemia, hepatotoxicity and cardiomyopathy) limit its use.

In contrast, ECP has an excellent safety and toxicity profile, even in patients using it long term. Experience with a similar dosing schedule has shown an excellent safety profile. In a Phase 2 randomized study of ECP versus no ECP in chronic GVHD, Flowers et al treated 48 patients with ECP three times weekly on week 1, and then twice weekly from weeks 2 through 12. Treatments were tapered thereafter according to response, and there was no difference in the incidence of adverse events between patients receiving ECP (n=48) and the control arm (n=47). Infections, particularly pneumonia, were the main adverse event, likely related to chronic GVHD itself. Couriel et al treated 71 patients with 2-4 treatments per week, with taper according to response. Only 4 patients developed toxicity that was mild, reversible and did not require discontinuation of therapy. These events included: abdominal pain, variations in blood pressure and fever. Jagasia et al , and Greinix et al used similar treatment schedules in 64 and 59 patients respectively, with no reported toxicities. Abreu et al treated 28 patients with Crohn's Disease twice weekly for the first 4 weeks, and then twice weekly every other week for 24 weeks. Only 2 patients required discontinuation for adverse events attributed to ECP, including nausea, malaise and fever with an increase in CRP. Again, these adverse events are difficult to separate from the manifestations of the disease, and the authors conclude that the treatment was well tolerated. In a UK Consensus Statement on the use of ECP in GVHD (Scarisbrick et al), the expert panel reported separately on schedules for GVHD and those used for CTCL. The reason for this was that the "accelerated" regimen was reported to gain rapid control of GVHD with 2 to 3 consecutive treatments every 1 to 3 weeks. Considering MS is an autoimmune disorder, we opted for the schedules more commonly used in other autoimmune diseases like chronic GVHD or Crohn's Disease.

If ECP is proven to be therapeutically efficacious in SPMS, it will revolutionize the treatment of that disorder. Intravenous methylprednisolone pulses will be used in the comparator arm. Pulse corticosteroids are commonly used as an adjunctive therapy or monotherapy to manage symptoms in SPMS (Zephir H et al. 2005) A randomized, controlled, single blind phase II clinical trial of regular pulses of intravenous methylprednisolone administered to MS patients over 5 years showed beneficial effects including prevention or delay of whole brain atrophy and disability progression, and suppression of T1-weighted MRI lesion formation (Zivodinov, et al. 2001). Furthermore, prolonged treatment with pulsed intravenous methylprednisolone was safe and well tolerated. Additionally, with the current design, patients who did receive mitoxantrone prior to accrual will still be able to participate in this study, unless they received treatment with it in the last two years.

Patients must be at least 18 years of age and must be able to provide informed consent.

4. STUDY POPULATION

The study population will consist of patients with SPMS. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

1. Patients with SPMS based on the Recommended Diagnostic Criteria for MS and clinical course. Secondary progression is defined by a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses.
2. Demonstrate EDSS scores between 3 to 6.5 at screening.
3. Documented EDSS progression in the 2 years prior to screening of 1 point or greater for patients with an EDSS score less than 6 at baseline, and greater than or equal to 0.5 for patients with an EDSS score greater than or equal to 6.0 at baseline. If documented EDSS scores are not available, a written summary of the clinical evidence of disability progression over the last 2 years, and retrospective assessment of EDSS score from data in the medical records, must be submitted for review by the principal investigators.
4. Documented absence of clinical relapse within 2 years of screening
5. Age ≥ 18 ≤ 75 years
6. Weight > 40≤ 150 kg.
7. Absolute Neutrophil count ≥ 2,000 per μL
8. Hematocrit ≥ 28 % and platelet count > 100,000 per μL (with or without transfusion support)
9. Willingness to use at least 1 reliable method of birth control (e.g. abstinence, oral contraceptives, intrauterine devices, barrier method with spermicide, or surgical sterilization) throughout the study for all men and women of childbearing potential
10. Willingness to participate in all study visits and procedures, as outlined in the informed consent
11. Patients able to give informed consent.
12. Patients must have adequate peripheral venous access to initiate ECP therapy.

4.2 Exclusion Criteria

1. Absolute medical contraindication to corticosteroid treatment
2. Absolute medical contraindication to receive ECP
3. Clinical relapse within 2 years of screening
4. Laboratory evidence of any of the following:
    a. WBC < 2,000 cells per uL
    b. Serum transaminase levels > x 2 UNL
    c. Creatinine Clearance < 60 mL/min
    d. HgbA1C > 6%

5. Concurrent diagnosis of a neurological condition that would interfere with the assessment of MS, or an autoimmune disease or inflammatory condition that is chronically treated with immunosuppressive agents, including systemic corticosteroids.
6. Evidence of known infection with human immunodeficiency virus (HIV) or active (not including latent) Hepatitis B (laboratory testing is not required if virus status is already known)
7. Uncontrolled infection requiring treatment at study entry
8. Hypersensitivity or allergy to psoralen (methoxalen)
9. Hypersensitivity or allergy to both heparin and citrate products (If hypersensitive or allergic to only one of these products, exclusion does not apply)
10. Inability to tolerate fluid changes associated with ECP (e.g. inadequate renal, hepatic, pulmonary and cardiac function leading to enable patient to tolerate extracorporeal volume shifts associated with ECP)
11. Presence of aphakia or photosensitive disease (systemic lupus erythematosis, porphyrias, albinism, etc.)
12. Women who are pregnant and/or lactating.
13. Use of any investigational drug/treatment at the time of enrollment or within the previous 60 days, or five elimination half-lives, or until the expected pharmodynamic effect has returned to baseline, whichever is longer.
14. Initiation of dalfampridine or change in the dose of dalfampridine within 6 months prior to randomization
15. Treatment with any of the medications or procedures listed below:
    - Glatiramer acetate, interferon-beta, fingolimod, teriflunomide or dimethylfumarate within 3 months prior to randomization
    - Natalizumab within 3 months prior to randomization
    - Cyclophosphamide within 1 year prior to randomization
    - Mitoxantrone within 1 years prior to randomization
    - Rituximab within 6 months prior to randomization
    - Ofatumumab, ocrelizumab, cladribine, daclizumab within 2 years prior to randomization
    - Intravenous immunoglobulin within 6 months prior to randomization
    - Plasmapheresis within 6 months prior to randomization
16. Corticosteroids within 3 months prior to screening, with the following exceptions: Topical ointments or creams, or eye drops that contain corticosteroids; Intranasal Steroids or Oral Steroids given in a single dose as a premedication for a procedure such as gadolinium-enhanced MRI.
17. Inability to undergo MRI scans
18. Contraindication to gadolinium due to past allergic, hypersensitive or adverse reaction or impaired renal function. Patients receiving a steroid prep prior to Gadolinium administration due to history of hypersensitivity or allergy to other agents or due to prior mild reaction to Gadolinium will not be excluded from the study.Any other disease or

condition which, in the opinion of the investigator, could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with study procedures.

19. Poor venous access
20. Previous history of skin cancer, leukemia/lymphoma/myeloma or bone marrow transplant.
21. Patients taking Coumadin who are unable to switch from oral anticoagulants to enoxaparin.
22. Heparin-induced thrombocytopenia
23. Poor cardiac function
24. Severe hypotension

5. PATIENT WITHDRAWAL AND REPLACEMENT

Patients may withdraw from the study at any time without penalty and for any reason without prejudice to his or her future medical care.

Patients must be withdrawn under the following circumstances:

- The patient withdraws consent
- Pregnancy (see Section 8.2.2.9)
- Unacceptable toxicity including patients on corticosteroids who develop psychosis or aseptic necrosis of the femoral head

Patients may be required to withdraw after discussion with the investigator for the following reasons:

- AE(s)
- At the discretion of the investigator
- Violation of eligibility criteria
- Deviation from the treatment plan specified in the protocol (e.g., incorrect administration of the study drug, failure to attend study visits, etc.)
- The treating physician can withdraw the patient from the study at any time and for any medical reason that he/she deems necessary
- The patient has a right to withdraw at any time, for any medical or other reasons.
- Patients who experience a clinical relapse (defined as neurological event characterized by new or worsening symptoms lasting 48 hours after a stable period of at least 30 days and is considered in the judgment of the investigator to be a clinical relapse). Patients who fail therapy will be off study, and further therapy will be at the discretion of the treating neurologist. The study will not cover any form of therapy after the patient is off study.
- Patients who have interval accumulation of T1 or T2 lesions and/ or gadolinium enhancing T1 lesions on the month 6 MRI scan
- In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the case report form (CRF) or similar.

Withdrawn patients will be replaced.

6. TREATMENT

6.1 Control Arm: Corticosteroid Treatment

Patients randomized to the control arm will receive corticosteroids in Pulses of 1 gram of intravenous methylprednisolone every 4 Weeks for 52 Weeks.

6.2 Study Arm: Extracorporeal Photopheresis

ECP will administered according to the following schedule:

Study Arm: Weeks 1-8: 3 times per week

Weeks 9-16: Twice per week

Weeks 17-36: Treatment on two consecutive days every 2 weeks (or optionally, one treatment per week)

Weeks 37-43: Once every 2 weeks

Weeks 44-52: Once every 4 Weeks

The CELLEX® System are integrated photopheresis systems that are approved in US and Europe, and marked specifically to perform photopheresis. With the CELLEX® System, whole blood is drawn from the patient, centrifuged and separated into its components: plasma, white blood cells, and red blood cells. The white blood cells and a portion of the plasma are collected in a separate chamber for treatment. The remaining plasma and red blood cells are returned to the patient untreated. This collection process is repeated over several cycles. The buffy coat suspension of white blood cells is then exposed to a predetermined amount of UVA light (photo activation) after being inoculated with UVADEX® (methoxsalen) Sterile Solution. Following the photo activation of the buffy coat suspension, the treated cells are returned to the patient.

Every attempt should be made to process 1500-2000 mL of blood during each treatment.

UVADEX® (methoxsalen) Sterile Solution is supplied in a 10 mL single-use vial. Each mL of solution contains 20 mcg of UVADEX® (methoxsalen) Sterile Solution. Each vial contains 10 mL of UVADEX® (methoxsalen) Sterile Solution, which is more drug than necessary for most treatments. However, the vials are designed for a single use. Therefore, there will be surplus of drug remaining in the vial at the conclusion of each treatment. Study center staff should NOT attempt to reuse any portion of this unused study drug once the seal has been compromised. The remaining UVADEX® (methoxsalen) Sterile Solution should be discarded after verification of dose by the study monitor as per study reference manual.

In the ECP process, UVADEX® (methoxsalen) Sterile Solution will be injected directly into the Recirculation Bag of the extracorporeal circuit after completion of the buffy coat collection, just prior to initiating photo activation. The dose of UVADEX® (methoxsalen) Sterile Solution used to inoculate these cells will be calculated based on the treatment volume collected during the plasma/buffy coat collection process, using the following formula:

Treatment Volume* in mL × 0.017 = Dose of UVADEX® (methoxsalen) Sterile Solution (in mL) required for administration into the recirculation bag

*As displayed on the CELLEX® System screen

Example: If 240 mL of the treatment volume is collected, the dose administered equals:

- (240 mL) x (0.017) = 4.08 mL
- 4.08 rounded to the nearest tenth is 4.1 mL

Therefore, a dose of 4.1 mL of UVADEX® (methoxsalen) Sterile Solution should be administered to the recirculation bag.

After the cells are inoculated with UVADEX® (methoxsalen) Sterile Solution, the buffy coat/plasma suspension is irradiated with ultraviolet-A light and then reinfused back into the patient.

For further information, please refer to the Investigator's Brochure.

7. STUDY PRODUCT

7.1 Identity

Extracorporeal Photopheresis procedural kits and UVADEX® (methoxsalen) Sterile Solution will be supplied by Therakos, Inc. at no cost. A CELLEX® System) must be available for treatment of study patients for the duration of the study.

THERAKOS Photopheresis System

The CELLEX® System is an integrated photopheresis systems that are approved in US and Europe, and marked specifically to perform photopheresis.

Patients in the ECP arm will have all of their ECP treatments with the same CELLEX® System.

For further information, please refer to the Investigator's Brochure.

In this protocol, UVADEX® (methoxsalen) Sterile Solution will be used in conjunction with the CELLEX® System. Please refer to the Operator's Manual for complete information and instructions for operating the CELLEX® Systems (https://therakos.com). The Therakos ® Photopheresis Systems and kits will be ancillary clinical supplies.

7.1.1 UVADEX® (methoxsalen) Sterile Solution

The active ingredient in UVADEX® (methoxsalen) Sterile Solution is 8-methoxypsoralen (methoxsalen). Methoxsalen is a naturally occurring photoactive substance found in the seed of the Ammi majus (umbelliferae plant). It belongs to a class of compounds known as psoralens or furocoumarins. The chemical name is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one. The formulation of the drug is a sterile liquid at a concentration of 20 mcg/mL in a 10 mL vial. A complete description of the pharmacokinetic activity of methoxsalen is available in the Investigator's Brochure.

Systemic exposure to UVADEX® (methoxsalen) Sterile Solution following ECP is minimal. The total dose of methoxsalen used to inoculate these cells is less than 1/200th of the oral dose used in conjunction with the UVAR XTS® System. Plasma levels obtained as part of other clinical studies have shown no detectable level (<10 ng/mL) 30 minutes after the reinfusion of the treated cell suspension containing the UVADEX® (methoxsalen) in >75% of patients.

Adverse events associated with the ECPs process during CTCL clinical trials include venous access complications, transient fever and worsening of the underlying CTCL skin rash and transient hypotension associated with hypovolemia. A complete description of the AEs documented in studies using UVADEX® (methoxsalen) Sterile Solution is provided in the Investigator's Brochure.

UVADEX® (methoxsalen) Sterile Solution is currently approved in the US, UK, Germany, and Austria for use in the palliative treatment of the skin manifestations of CTCL unresponsive to other therapies.

7.2 Packaging, Labeling and Storage

UVADEX® (methoxsalen) Sterile Solution is packaged in 10 mL, 13 mm, United States Pharmacopeia Type I borosilicate amber glass vials. The closure is a 13 mm, gray butyl rubber stopper laminated with 0.1 mm fluorocarbon polymer film. A 13 mm aluminum flip-off cap, with a clear lacquer foil and purple plastic flip-off button, is used to seal the stoppered vials.

UVADEX® (methoxsalen) Sterile Solution must be stored at between 15°C and 30°C (USA labeling) or less than 25°C (European labeling).

Procedural kits should be stored in a secure location, at room temperature, and labeled with "Clinical Trial Use Only".

UVADEX® (methoxsalen) Sterile Solution will be labeled according to the US regulations, and will be labeled as "Investigational Product".

Corticosteroids will be obtained from the Pharmacy at the University of Michigan.

7.3 Drug Accountability

7.3.1 Shipment and Receipt

At the time clinical supplies UVADEX® (methoxsalen) Sterile Solution and Procedural Kits are received at the University of Michigan, a "Receipt of Investigational Drug/Device" form will be completed. This receipt will include the total number of supplies received, the date received, and the condition of the supplies at time of receipt. This form is to be signed and dated by the staff member appointed by the investigator to account for investigational supplies. The white copy of this form is to be returned to the Therakos clinical department or its designated representative. The yellow copy of the form should be kept at the site and filed with the investigational drug/device log.

In the event that drug or devices do not arrive at the study center by the date indicated on the form or the number of investigational products received at the site does not correspond with the number indicated on the form, Therakos clinical department should be notified immediately.

7.3.2 Accountability Logs

An accurate record of all supplies received and used at the University of Michigan should be maintained and updated regularly. Procedural kit use will be recorded on the Investigational Device Inventory Log. UVADEX® (methoxsalen) Sterile Solution use will be recorded on the Investigational Drug Log. In the event that study drug or devices are damaged, an account should be made on the appropriate log.

At the conclusion of the study, all remaining procedural kits must be returned to the Therakos or destroyed at the site according to the clinical monitoring plan. Once all study products have been accounted for and verified by Therakos or its designated agent, unused vials of UVADEX® (methoxsalen) Sterile Solution will be destroyed.

7.3.3 Investigational Device

An Investigational device, the CELLEX® System, is available at the University of Michigan.

7.4 Compliance

Study drug used, dosage administered, and intervals between visits will be recorded during the study.

7.5 Concomitant Medications

Any medication the patient takes other than the study drug, including herbal and other non-traditional remedies during the 52 Week study, is considered a concomitant medication. All concomitant medications must be recorded in the CRF. The following information must be

recorded in the CRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the CRF.

At Screening, patients will be asked what medications they have taken during the last 30 days and what concomitant medication they are taken. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

The following drugs/therapies are permitted at the investigator's discretion:

- Medications to prevent infection (pneumocystis, viruses and fungal organisms, etc.) per institutional practice.
- Venous access for ECP (at investigator's discretion and per institutional practice).
- Systemic steroids may be administered for clinical relapse or the emergence of gadolinium enhancing MRI lesions.

The following drugs/therapies are prohibited during the treatment period of the study:

- Tysabri® (natalizumab) or other intravenous DMA
- Initiation of dalfampridine or change in the dose of dalfampridine within 6 months prior to randomization
- Treatment with any of the medications or procedures listed below:
- Glatiramer acetate, interferon-beta, fingolimod, teriflunomide or dimethylfumarate within 3 months prior to randomization
- Natalizumab within 3 months prior to randomization
- Cyclophosphamide within 1year prior to randomization
- Mitoxantrone within 1 years prior to randomization
- Rituximab within 6 months prior to randomization,
- Ofatumumab, ocrelizumab, cladribine, daclizumab within 2 years prior to randomization
- Intravenous immunoglobulin within 6 months prior to randomization
- Plasmapheresis within 1 year prior to randomization

Corticosteroids within 3 months prior to screeing, with the following exceptions: Topical ointments or creams, or eye drops that contain corticosteroids; Intranasal Steroids or Oral Steroids given in a single dose as a premedication for a procedure such as gadolinium-enhanced MRI.

8. PARAMETERS AND METHODS OF ASSESSMENT

8.1 Efficacy Parameters

8.1.1 MSFC

The MSFC components can be found in Appendix 1. This scoring system should be administered after reading the manual to ensure that a standardized format should be followed. The MSFC consists of the following components and should be done in the following order:

1. Trial 1: Timed 25-Foot Walk
2. Trial 2: Timed 25 Foot Walk
3. Trial 1: Dominant Hand, 9-HPT
4. Trial 2: Dominant Hand, 9-HPT
5. Trial 1: Non-Dominant Hand, 9-HPT
6. Trial 2: Non-Dominant Hand, 9-HPT
7. PASAT-3”

An individual component should be discontinued only if the patient meets the discontinue criteria for that component. Other components should still be administered.

Every effort should be made to use the same testing room and the same designated area for the Timed 25 Foot Walk at every visit. It is essential that that the potential for external distraction be kept to a minimum. If the space designated for the Timed 25 Foot Walk is in a public hallway, complete privacy may be impossible, however, every attempt must be made to keep the patient’s path clear of obstacles (human and inanimate). No one other than the examiner and the patient should be in the testing room during 9-HPT and PASAT. The first time a subject takes the PASAT, practice sequences are initially administered a maximum of 3 times.

The response definitions are as below:

An MSFC score is created from the tests done above. Details can be found in the publication referenced (Fischer et al). The composite consists of Z score from the components tested and compared using normals to standardize the scored. The MSFCS is a continuous variable that can be used as any numerical variable in analyses. The value is subject to tests appropriate for continuous variables, such as t-tests, Analysis of variance and regression analysis as well as nonparametric test. A composite based on such Z-scores can also measure change in performance over time. By computing the composite at one point in time and measuring the patient at a later point in time, the arithmetic difference between MSFC scores can be used to measure improvement or worsening.

8.1.2 EDSS

The EDSS form can be found in Appendix 2. The scores are calculated from the Functional System Score (FSS). EDSS and FSS will be determined by a single neurologist at baseline, and every 3 months through 2 years.

The EDSS is an ordinal scale with a 0.5-point increments ranging from 0-10.0. (increasing score indicates worsening) and based largely on ambulatory impairment in its middle range (EDSS 4.5-7.5 points).

0= normal neurological exam
10-death due to MS
Score 6 is still ambulatory with assistance
Score of 7 means patient must use a wheelchair.

8.1.3 MRI

All patients will be evaluated with cranial MRI examination on a 1.5 tesla strength magnet at baseline and months 6 and 12 using the following sequences: axial T2-weighted, axial and sagittal T1 weighted, axial and sagittal fluid attenuated inversion recovery (FLAIR), post Gadolinium axial and coronal T1 weighted images. The total number of gadolinium enhancing T1-weighted lesions and interval changes in the number and size of T-weighted, FLAIR and T1-weighted lesions will be determined by a board certified neuro-radiologist.

8.2 Safety Parameters

8.2.1 Immunological Studies

The following immune parameters will be measured at baseline, and again at 3, 6, 9 and 12 months. Frequency of myelin basic protein-specific IFNγ or IL-17 producing PBMC, Frequency of tetanus toxoid –specific IFNγ or IL-17 producing PBMC, plasma levels of IFNγ, IL-17, IL-4, IL-10, IL-12, IL-21, IL-23, CCL2, GROα, CXCL8, CXCL10, CCL11, CXCL13, GM-CSF, G-CSF and neutrophil elastase. Additional inflammatory molecules might be measured based on preliminary findings.

8.2.2 Adverse Events

8.2.2.1 Collection of Adverse Events

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by interval open questioning.

8.2.2.2 Definitions

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinical significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the CRF. Underlying disease worsening (MS), hospitalization for routine study activities, and abnormal laboratory results associated with MS, will not be considered as AEs. Relapse of underlying malignancy will not be considered as an AE/SAE but will be captured and analyzed separately. MS will not be considered as an AE, unless it meets any of the seriousness criteria, in

particular hospitalization or death. Concomitant illnesses, which existed prior to entry into the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the CRF on the Medical History or appropriate page. AEs will be captured after informed consent signed until 30 days post the completion of the last intervention. (Week 52).

8.2.2.3 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to the following categories.

8.2.2.3.1 Seriousness

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  this means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

8.2.2.3.2 Intensity

The intensity of each AE must be assessed by the investigator using one of the following categories, and recorded in the CRF:

- Mild: An AE that does not interfere with usual activities;
- Moderate: An AE that interferes with usual activities;
- Severe: An AE that prevents usual activities.

8.2.2.3.3 Causality

The investigator will assess the causality / relationship between the study treatment groups (corticosteroids or ECP) and the AE and record that assessment in the CRF.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the CRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug/device will be described in terms of:

- Probable: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug/device.
  - Could not be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Disappears or decreases on cessation or reduction in dose of the study drug/device.

  - Follows a known pattern of response to the study drug/device.
  - Reappears or worsens upon rechallenge.
- Possible: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug/device.
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Follows a known pattern of response to the study drug/device.
- Unlikely: the AE
  - Does not follow a reasonable temporal sequence from administration of the study drug/device.
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the subject.
  - Does not follow a known pattern of response to the study drug/device.
  - Does not reappear or worsen upon rechallenge.
- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the study drug/device.

For SAEs related or possibly related to ECP, the investigators will also provide an assessment of whether the SAE is related to the drug, UVADEX® (methoxsalen) Sterile Solution or the procedure/device.

8.2.2.4 Recording Adverse Events

Adverse event reporting will extend from signing of informed consent until completion of study (Week 52) or 30 days after the last study intervention. Adverse events occurring after the end of the study should be reported to the Sponsor by the investigator if the investigator considers there is a causal relationship with the study treatment.

All AEs (including AEs resulting from active standard of care medication and study instrument), regardless of the relationship to study drug, will be recorded in the CRF.

In addition, the technician performing the ECP procedure will observe and record any AEs that occur during the procedure. Treatment will be stopped if the patient cannot tolerate the procedure.

All AE reports should contain a brief description of the event, date of onset, date of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

8.2.2.5 Reporting Serious Adverse Events

All SAEs, regardless of relationship to the study agent(s) or study procedure(s), must be reported to the investigator, or his designee, within 24 hours of observation or notification of the event. Instructions for reporting an SAE are provided in this section. The name(s) and contact details of the individual(s) who should be contacted regarding safety issues or questions regarding the study are also included in the Box on page 39 and in the Study Reference Manual.

The Investigator will review each SAE report and the investigator will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Investigator will evaluate the expectedness according to the reference document (Investigator Brochure, Device

Instructions for Use (IFC) and the informed consent document). Based on the Investigator's assessment of the event, a decision will be made concerning the need for further action.

Hospitalization due to MS progression will be considered as an SAE. Hospitalization for an elective or planned procedure to treat a preexisting condition will not be considered as an SAE unless it results in one of the other outcomes listed above. Hospitalizations for study agent administration only will not be considered as SAEs. Details for the reporting of suspected unexpected serious adverse reactions (SUSARs) can be found in Section 8.2.2.7.

All SAEs will be recorded from signing of informed consent until the end of the study (Week 52).

Safety contact for study:

Safety Line Number: 734-936-8785
Safety Fax Line:
Email: Daniel Couriel <dcouriel@med.umich.edu>
Investigator Responsible for SAE reporting: Dr. Daniel R. Couriel

SAE reporting Instructions:

- Fax the SAE form and any supporting documentation to the Investigator.
- Telephone the Investigator to confirm that you have faxed a SAE form
- Provide investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.

The minimum information required for an initial report is:

- Sender of report (name, address of investigator).
- Patient identification (screening/randomization number, initials, NOT patient name).
- Protocol number.
- Description of SAE.
- Causality assessment.

After receipt of the initial report, the Investigator will review the information and, if necessary, contact the involved physician to obtain further information for assessment of the event. The Investigator or his designee will be responsible for all information processing and reporting according to legal requirements following ICH E6 guidelines. The Sponsor-Investigator will be responsible for all safety reporting to the FDA. Details for the reporting of SUSARs and UADE's can be found in Section 8.2.2.7

8.2.2.6 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up or event is unlikely to resolve.

Data and Safety Monitoring Board (DSMB)

To protect the interests of research subjects and ensure that they are not exposed to undue risk, this trial will be monitored by an independent DSMB, consisting of appropriate medical experts

with no formal involvement with the subjects or the investigation and will function independently of the Clinical Study Team.

The Blood and Marrow Transplantation DSMB meets on a quarterly basis to review all the SAEs (unblinded); the most frequent AEs (blinded aggregate data) and laboratory data of interest and will make recommendation to the study team regarding the safety aspect of the study. Based on the safety data, the DSMB may recommend that the trial be modified or stopped or may request an interim analysis for efficacy.

8.2.2.7 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study drug, and unexpected (defined as the nature or severity of event, which is not consistent with the applicable product information [i.e. Investigator's Brochure]) (SUSARs) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, regulatory authorities and ethics committees will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, regulatory authorities and ethics committees will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the investigators of relevant information about SUSARs that could adversely affect the safety of patients in a timely fashion. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and ethics committees responsible for the trial. These updates will include information on SUSARs and other relevant safety findings.

Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of the subjects.

UADEs will be reported to the FDA as outlined nad required under 21 CFR p812.150(b)(1).

8.2.2.8 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the investigational drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the investigational product may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the investigator to the FDA on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The investigator must follow up and document the course and the outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Sponsor-Investigator to the FDA on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a spouse of a male study subject who has been exposed to the Investigational Medicinal Product becomes pregnant, every effort should be made to monitor the pregnancy and outcome of pregnancy. A separate informed consent will be provided for the spouse prior to any data being collected regarding the pregnancy.

8.2.2.9 Complaint Reporting/Device Malfunctions

All device malfunctions should be reported to Therakos' support Hotline. The customer technical support phone numbers are 877-865-6850 in the US. Dialer should identify his/her involvement in this clinical study.

Device malfunctions do not have to be recorded in the CRF. Any AEs resulting from the malfunction will be reported in the CRF per Section 8.2.2.

8.2.3 Laboratory Parameters

Clinical laboratory assessments will be performed by the UM Hospital Clinical Laboratory at the University of Michigan. Research laboratory studies to measure immunological parameters will be conducted the Neuroimmunology Research Laboratory in the Department of Neurology at the University of Michigan (Dr. Segal, Director).

Blood samples should be taken using standard venipuncture techniques. Blood samples should be processed according to the procedure described in the laboratory manual.

Laboratory parameters will be determined in accordance with the Schedule of Assessments on Table 2.

Table 1: Laboratory Assessments

Hematology:	Complete CBC
Chemistry:	Creatinine Glucose Triglycerides Urea Uric acid Bilirubin Cholesterol Sodium Potassium
Liver Function Tests	Alkaline phosphatase Aspartate transaminase Alanine transaminase
Immune Parameters	Myelin basic protein –specific IFNγ or IL-17 producing PBMC, Frequency of tetanus toxoid –specific IFNγ or IL-17 producing PBMC, plasma levels of IFNγ, IL-17, IL-4, IL-10, IL-12, IL-21, IL-23, CCL2, GROα, CXCL8, CXCL10, CCL11, CXCL13, GM-CSF, G-CSF and neutrophil elastase

Clinically significant laboratory abnormalities should be recorded as AEs according to investigator's judgment. The maximum total amount of blood that will be taken during the study from an individual patient for research studies is 60 ml per blood draw. There will be a total of five blood draws, separated by intervals of 9 weeks or longer. Patients on ECP will have an additional blood draw of 5 ccs prior to every procedure to determine hematocrit and platelet count.

8.2.4 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Assessments (Table 2):

- Weight and Height (height will be measured only at Screening);
- Blood pressure (systolic and diastolic; mmHg);
- Heart rate (beats per minute);
- Body temperature (°C);
- Respiration rate (breaths per minute).

These variables should be collected after the patient has been sitting for 5 minutes.

8.2.5 Physical Examinations

A brief physical examinations will be performed in accordance with the Schedule of Assessments (Table 2).

8.2.6 Medical History and Interim History

A complete medical history will be performed at start of study and a briefer interim history performed at each visit.

9. STUDY CONDUCT

9.1 Schedule of Assessments

The schedule of assessments is shown in months, as it facilitates better comprehension, preventing potential errors, in the interpretation of the exact timing for each assessment. On the other hand, in order to facilitate integration with the weekly-based schedule of ECP, and also budget considerations, we use the following transformation between weeks and months when addressing the schedule of assessments:

a- 3 months: Week 12+/-2 week

b- 6 months: Week 24 +/-2week

c- 9 months: Week 36 +/-2 week

d- 12 months or 1 year: Week 52 +/- 1 month

The schedule of assessments is shown in Table 2.

Table 2: Schedule of Assessments

Procedures	Screening (-30days)	Baseline[5] (Week 2)	Month 3	Month 6	Month 9	12 months/1year	Til End of Study (evey 3 months through 2 years)[8]
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Vital Signs		X	X	X	X	X	
Medical History/ Interim History [1]	X	X	X	X	X	X	
Physical Examination		X	X	X	X	X	
MSFC[8]		X	X	X	X	X	X
EDSS[8]		X	X	X	X	X	X
MRI		X		X		X	
Pregnancy Test[2]	X						
Immune Parameters Measurement		X	X	X	X	X	
Clinical Laboratory Tests[3]	X	X				X	
Pre-study/Concomitant MedicationsMRI	X	XX	X	XX	X	XX	
Adverse Events	X	X	X	X	X	X	
Randomization to ECP[5,6] vs IVMP[7]	X						

[1] Including history of MS, progression from RRMS to onset of SPMS. A complete history at start of study and interim history at each visit.
[2]For women of childbearing potential.
[3] Both at screening and prior to each ECP procedure, a small amount of blood (2-4 teaspoons) will be drawn to evaluate CBC and chemistries.
[4]Subjects will be randomized at a 1:1 ratio to either ECP.or IVMP
[5]Patients should have ECP within 14 days of baseline visit.
[6]The frequency of ECP treatments will be:
Weeks 1-8: 3 x/ week
Weeks 9-16: 2x/week
Weeks 17-36: 2x/2 weeks
Weeks 37-43: 1x / every 2 weeks
Weeks 44-52: 1x/ every 4 Weeks
[7] Corticosteroid is administered on a pulse basis and consists of 1 gram of methylprednisolone I.V. every 4 Weeks for 52 Weeks.
[8]These test will occur every three month through 2 years.

9.2 Observations by Visit

Visits and assessments should occur within the schedule in Table 2 according to study. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

9.2.2 Screening

- If patient has had an appt with a physical exam in the last 30 days, that can be used for this screen.
- Obtain written informed consent.
- Verify inclusion and exclusion criteria
- Demographics and medical history
- MS Scoring and History
- Pregnancy test (for women of child-bearing potential patients only), whether to be done on urine or blood will be at investigator's discretion or per institutional practice.
- Collect blood sample for laboratory assessment (Table 1) (note: samples will be sent to local laboratories)
- Record pre-study/concomitant medication
- Randomization 1:1

9.2.3 Baseline (Week 1)

A baseline visit should be performed and 1st ECP scheduled within 14days.

- Physical examination.
- Interim History
- Vital signs.
- MSFC
- MRI
- EDSS
- Blood for immune parameters (sent to the University of Michigan Neuroimmunology Research Laboratory)
- Collect blood sample for laboratory assessment (Table 1)
- Record concomitant medication.
- Assessment of pre-treatment events (AEs occurring from ICF signed to baseline visit).
- Start ECP within 14 days of baseline as defined in the schedule of assessments

9.2.4 Month 3/Week 12

- At this point patients who are assigned to ECP arm will have been tapered from 3 treatments weekly to two treatments weekly.
- Patients randomized to the ECP arm must receive their first ECP treatment within 14 days of baseline visit.
- Before ECP, on each day of treatment, blood samples will be collected for CBC or other clinical routine testing as needed, and no less that weekly.
- Patients admitted to the corticosteroid arm will receive a treatment once every month as stated above

- The following will also be performed at this time point: Interim history, vital signs, physical exam.
- Blood for immune parameters (sent to the UM Neuroimmunology Research Laboratory)
- MSFC
- EDSS
- Adverse Events
- Concomitant Medications

9.2.5 Month 6/Week 24

At this point patients on ECP will have been tapered to two treatments (on 2 consecutive days) every 2 weeks. If preferred, patients may be given the option of receiving one weekly treatment (as opposed to two treatments on 2 consecutive days) a schedule modification

- Before ECP on each day of treatment blood samples will be collected for the laboratory tests on Table 1 and sent to the University of Michigan Clinical Laboratory
- Patients admitted to the corticosteroid arm will receive a treatment once every month as stated above
- The following will also be performed at this time point:
  - Interim history, vital signs, physical exam.
  - Blood for immune parameters (sent to the UM Neuroimmunology Research Laboratory)
  - MSFC
  - EDSS
  - Adverse Events
  - Concomitant Medications
  - MRI with Gadolinium

9.2.6 Month 9/ Week 36

On weeks 37-43, ECP-treated patients transition to one treatment every two weeks and for

Patients admitted to the corticosteroid arm will receive a treatment once every month

- Before ECP on each day of treatment blood samples will be collected for the laboratory tests on Table 1 and sent to the University of Michigan laboratory to perform testing as described above.
- Patients admitted to the corticosteroid arm will receive a treatment once every month as stated above
- The following will also be performed at this time point:
  - Interim history, vital signs, physical exam.
  - Blood for immune parameters (sent to the UM Neuroimmunology Research Laboratory)

- MSFC
- EDSS
- Adverse Events
- Concomitant Medications

9.2.7 Week 52 through the End of Study

- From Weeks 44-52, patients will receive one ECP treatment every 4 weeks
- Patients admitted to the corticosteroid arm will receive a treatment once every month
- Before ECP on each day of treatment blood samples will be collected for the tests outlined on Table 1
- The following will also be performed at this time point:
    - Interim history, vital signs, physical exam.
    - Blood for immune parameters (sent to the UM Neuroimmunology Research Laboratory)
    - MSFC(every 3 months through 2 years)
    - EDSS (every 3 months through 2 years)
    - Adverse Events
    - Concomitant Medications
    - MRI with Gadolinium

9.2.8 Early Termination Visit

Patients who withdraw from the study before Week 52 but at the time of a scheduled visit must complete Week 52 assessments. If a patient withdraws between scheduled visits, the patient must come into the clinic to perform the Week 52 assessments. This study does not allow for cross-over between study group to control group or vice-versa while on study.

10. STATISTICAL METHODS

Any deviations from the planned analyses will be described and justified in the final integrated study report.

10.1 Planned Sample Size and Number of Study Centers

It is planned to recruit approximately 66 patients (33 per treatment arm). This is a single center study.
Patients will be randomized on a 1:1 basis to corticosteroids or ECP arm.
Patients randomized to the ECP treatment arm must receive their first treatment within 5 days of the baseline visit.
For the randomization of patients, the investigator will use an Interactive Voice Response System (IVRS). Details can be found in the trial master file. IVRS will assign patients to a treatment group based on the pre-defined randomization list.

10.2 Efficacy Analyses

10.2.1 Analysis of Primary Endpoint

The primary end point is the proportion of subjects with no evidence of disease progression, as defined below, at Week 52. Intent to treat approach will be used. Progression is defined as a minimum change from baseline in one or more of the following parameters:

- 20% or greater increase in the timed 25 foot walk
- 20% or greater increase in the 9 hole peg test
- 1 point or greater increase in EDSS score in subjects with baseline EDSS scores between 3 and 5.5
- 0.5 point or greater increase in EDSS score in subjects with baseline EDSS scores equal to or greater than 6

The proportion of subjects who have not progressed clinically, based on the above criteria, at Week 52 after initiation of study therapy will be compared between treatment groups using the Chi-square test.
The early drop-outs, including patients who withdraw will be considered as non-responders.

10.2.2 Analysis of Secondary Endpoints

The secondary endpoints include:

- Change in Plasma levels of Immunological Factors and Frequencies of IFNγ and IL-17 MBP-specific PBMC at months 3, 6, 9 and 12 compared with baseline
- MSFC 3 dimensional composite z-score at every 3 month time point through 2 years compared to baseline
- Expanded Disability Status Scale (EDSS) score at every 3 month time point through 2 years compared to baseline
- Percentage of subjects with improvement (as defined for the primary endpoint) at months 3, 6, 9 and 12 compared to baseline
- Occurrence of clinical relapse at any point in the study

- Interval change in T2 lesion number and volume on MRI scans obtained at months 6 and 12 compared to baseline
- The number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12 compared to baseline
- Interval change in the number and volume of gadolinium enhancing lesions on MRI scans obtained at months 6 and 12 compared to baseline.
- Toxicity and Adverse events in both arms

For continuous outcomes, two-sample t-tests or Wilcoxon rank sum tests will be used to compare the treatment arms. For categorical outcomes, Chi-square tests or Fisher's exact test will be used to compare the treatment arms. The proportion of subjects who experience adverse events and serious adverse events will be summarized by treatment group descriptively; no inferential tests will be performed.

10.2.3 Interim Analyses

There will not be any planned interim analyses for efficacy assessments.

10.3 Safety Analyses

Safety parameters for each patient include vital signs, laboratory testing, including chemistry panel and complete blood count, and AE reporting, including AEs resulting from active concomitant standard of care medication. These parameters will be tabulated in line listings along with basic demographic information such as sex and age by clinical site and by treatment arms.

10.4 Determination of Sample Size

Assuming that the proportion of subjects in the corticosteroid treatment who show no evidence of clinical progression at 52 (12 months) is 30%, 66 subjects (33 per treatment arm) provides at least 80% power to detect a treatment difference of 30% (i.e., 60% of the ECP treated subjects will show no evidence of clinical progression at 12 months), based on the normal approximation of the binomial distribution and a one-sided Type I error of 5%.

11. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Data Quality Assurance

This is an investigator initiated research protocol. The investigator will assure that the study will be conducted according to Good Clinical Practice Guidelines as outlined in ICH E6. The investigative team will prepare the CRFs needed for the study.

The investigator will prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

11.2 Case Report Forms and Source Documentation

The CRF's will be the basis for data entry for this study. The investigator will assure that the data are correctly entered into the CRFs and the study monitor for the study will assure that this corresponds to the source documentation. Any discrepancies will be corrected as needed and signed off by the investigator.

11.2.1 Data Collection

Access and right to the CRFs will be carefully controlled and configured according to each individual's role throughout the study. In general, only the investigator and authorized staff will be able to enter data and make corrections in the CRFs.

The CRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the CRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The investigator must verify that all data entries in the CRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the CRF. Manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the investigator will be required to sign off the clinical data

Data about all study drugs dispensed to the patient will be tracked on CRFs.

11.3 Access to Source Data

During the course of the study, a designated clinical monitor will review protocol compliance, compare CRFs and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the CRFs for completeness and clarity, and crosschecking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities, Institutional Review Boards (IRBs) may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

11.4 Data Processing

All data will be entered by site personnel into the CRFs.

The Data Cleaning Specification, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data, and also include rules for data handling (e.g. what fields are entered for Screen Failures).

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The versions of the coding dictionaries can be obtained or provided by Therakos.

11.5 Archiving Study Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after final publication and until there are no pending or contemplated publication or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

11.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the study will be conducted in accordance with the principles of the Good Clinical Practice guidelines of the ICH, and of the Declaration of Helsinki (1996). The study also will be carried out in keeping with local legal requirements.

11.7 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the IRB requests, patients that are currently enrolled in the study will be re-consented with the revised consent.

11.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

The protocol and IRB approval will be submitted to the Investigational Device Exemption (IDE) for the product to the FDA for notification/comment.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will also be submitted to IDE under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.9 Duration of the Study

For an individual patient, the maximum duration of the study for each patient will be up to 52 weeks (excluding up to 1 week screening). The total study is expected to last 2 years.

11.10 Premature Termination of the Study

If the Sponsor-Investigator, or the DSMB becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor-Investigator's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure to enroll patients at an acceptable rate;

11.11 Confidentiality

All study findings and documents will be regarded as confidential.

The anonymity of participating patients must be maintained. Patients will be identified on CRFs and other documents by their patient number, initials and/or birth date, not by name.

11.12 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – regulatory authorities, investigators and IRB.

A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

11.13 Publication Policy

Since this is an investigator-sponsored research, the Investigator will publish the records as per the policy of the University of Michigan.

11.14 Monitoring of the Study

To assure adequate protection of the rights of human subjects, per 21 CFR §812.40, 812.43 and 812.46, this study will be monitored by the University of Michigan Institute of Clinical and health research (MICHR) Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. A site activation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the Study Team, Steering Committee or Data and Safety Monitoring Board (DSMB).

The established monitoring plan will ensure the quality and integrity of the data throughout the study conduct to verify adherence to the protocol, completeness and accuracy of study data and samples collected, dispensing and inventory of the device, and compliance with regulations.

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13. APPENDICES

13.1 Appendix 1 MSFC Forms

RECORD FORMS FOR THE
MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE

LOWER EXTREMITY FUNCTION: TIMED 25-FOOT WALK

Subject ID Number | Subject Initials | Visit Date: Day | Month | Year

TIMED 25-FOOT WALK

Did patient wear an AFO? ☐ Yes ☐ No

Was assistive device used? ☐ Yes ☐ No

Assistive device used *(mark one)*:

☐ Unilateral Assistance ☐ Cane ☐ Crutch

☐ Bilateral Assistance ☐ Cane ☐ Crutch ☐ Walker/Rollator

Trial 1

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡ _____

☐ Other ➡ _____

Trial 2

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡ _____

☐ Other ➡ _____

Did it take more than two attempts to get two successful trials? ☐ Yes ☐ No

If yes, please specify reasons(s) for more than two attempted trials:

_____

_____

ADMINISTRATION AND SCORING MANUAL FOR THE MSFC – REVISED OCT. 2001

UPPER EXTREMITY FUNCTION: NINE-HOLE PEG TEST (9-HPT)

Subject ID Number | Subject Initials | Visit Date: Day | Month | Year

9-HOLE PEG TEST

DOMINANT HAND *(Check one):* Right ☐ Left ☐

DOMINANT HAND

Trial 1

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify:

☐ Other ➡

Trial 2

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify:

☐ Other ➡

Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No
If Yes, please specify reason(s) for more than two attempted trials:

NON-DOMINANT HAND

Trial 1

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify:

☐ Other ➡

Trial 2

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify:

☐ Other ➡

Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No
If Yes, please specify reason(s) for more than two attempted trials:

COGNITIVE FUNCTION: PASAT - PRACTICE ITEMS	
Subject ID Number / Subject Initials	Visit Date: Day / Month / Year

PASAT Practice Items

RATE #1
(3 sec.)

9 + 1 10___	3 4___	5 8___	2 7___	6 8___	4 10___	9 13___	7 16___	1 8___	4 5___
9 + 1 10___	3 4___	5 8___	2 7___	6 8___	4 10___	9 13___	7 16___	1 8___	4 5___
9 + 1 10___	3 4___	5 8___	2 7___	6 8___	4 10___	9 13___	7 16___	1 8___	4 5___

PASAT Practice Items

RATE #2
(2 sec.)

3 + 8 11___	2 10___	7 9___	9 16___	1 10___	8 9___	5 13___	2 7___	6 8___	4 10___
3 + 8 11___	2 10___	7 9___	9 16___	1 10___	8 9___	5 13___	2 7___	6 8___	4 10___
3 + 8 11___	2 10___	7 9___	9 16___	1 10___	8 9___	5 13___	2 7___	6 8___	4 10___

COGNITIVE FUNCTION: PASAT - FORM A

Subject ID Number | Subject Initials | Visit Date: Day / Month / Year

RATE #1
(3 sec)

1 + 4	8	1	5	1	3	7	2	6	9
5____	12____	9____	6____	6____	4____	10____	9____	8____	15____
4	7	3	5	3	6	8	2	5	1
13____	11____	10____	8____	8____	9____	14____	10____	7____	6____
5	4	6	3	8	1	7	4	9	3
6____	9____	10____	9____	11____	9____	8____	11____	13____	12____
7	2	6	9	5	2	4	8	3	1
10____	9____	8____	15____	14____	7____	6____	12____	11____	4____
8	5	7	1	8	2	4	9	7	9
9____	13____	12____	8____	9____	10____	6____	13____	16____	16____
3	1	5	7	4	8	1	3	8	2
12____	4____	6____	12____	11____	12____	9____	4____	11____	10____

Total Correct (raw) = _____ Percent Correct = _____

RATE #2
(2 sec)

4 + 3	7	2	5	1	8	6	9	1	7
7____	10____	9____	7____	6____	9____	14____	15____	10____	8____
9	4	6	3	5	8	1	6	2	7
16____	13____	10____	9____	8____	13____	9____	7____	8____	9____
5	9	4	5	2	6	4	8	3	5
12____	14____	13____	9____	7____	8____	10____	12____	11____	8____
9	7	4	2	8	5	2	1	6	4
14____	16____	11____	6____	10____	13____	7____	3____	7____	10____
7	3	5	9	6	4	5	3	9	4
11____	10____	8____	14____	15____	10____	9____	8____	12____	13____
1	8	3	1	6	8	5	4	2	6
5____	9____	11____	4____	7____	14____	13____	9____	6____	8____

Total Correct (raw) = _____ Percent Correct = _____

FORMS FOR THE MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE

COGNITIVE FUNCTION: PASAT - FORM B

Subject ID Number | Subject Initials | Visit Date: Day | Month | Year

RATE #1
(3 sec)

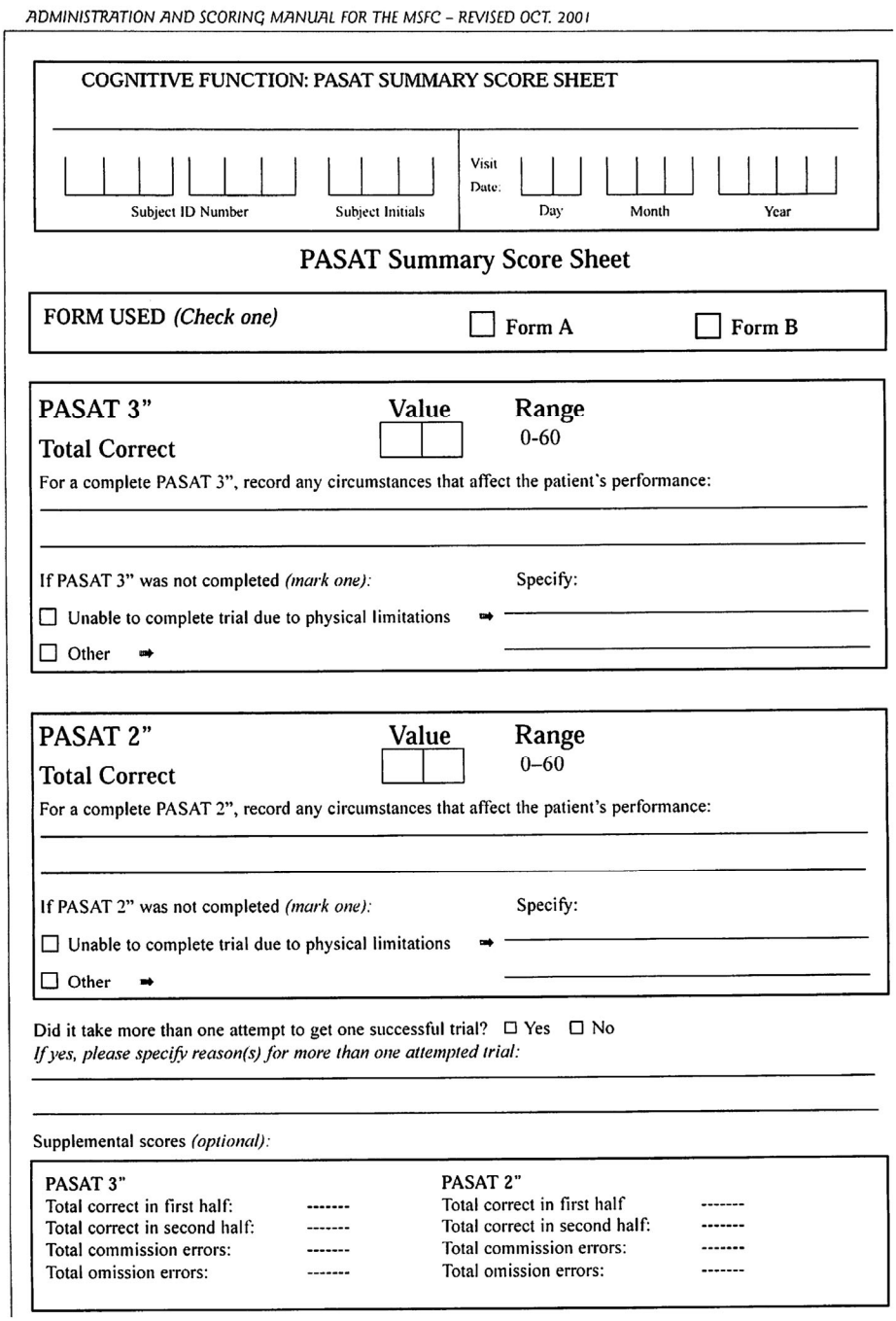
2 + 7 9____	5 12____	8 13____	2 10____	9 11____	6 15____	4 10____	1 5____	3 4____	6 9____
3 9____	6 9____	2 8____	8 10____	4 12____	9 13____	1 10____	6 7____	7 13____	2 9____
4 6____	1 5____	5 6____	7 12____	3 10____	9 12____	7 16____	2 9____	6 8____	8 14____
4 12____	2 6____	5 7____	8 13____	5 13____	9 14____	3 12____	7 10____	1 8____	4 5____
2 6____	4 6____	3 7____	6 9____	1 7____	7 8____	3 10____	8 11____	3 11____	9 12____
1 10____	3 4____	5 8____	2 7____	6 8____	4 10____	9 13____	7 16____	1 8____	4 5____

Total Correct (raw) = _____ Percent Correct = _____

RATE #2
(2 sec)

7 + 8 15____	6 14____	3 9____	7 10____	5 12____	9 14____	1 10____	2 3____	6 8____	8 14____
3 11____	6 9____	2 8____	5 7____	9 14____	7 16____	1 8____	8 9____	3 11____	6 9____
7 13____	4 11____	2 6____	5 7____	3 8____	8 11____	6 14____	2 8____	3 5____	7 10____
3 10____	5 8____	2 7____	8 10____	5 13____	3 8____	7 10____	4 11____	1 5____	5 6____
2 7____	4 6____	1 5____	6 7____	3 9____	9 12____	7 16____	1 8____	8 9____	4 12____
6 10____	2 8____	5 7____	8 13____	1 9____	9 10____	7 16____	2 9____	8 10____	3 11____

Total Correct (raw) = _____ Percent Correct = _____



ADMINISTRATION AND SCORING MANUAL FOR THE MSFC – REVISED OCT. 2001

COGNITIVE FUNCTION: PASAT SUMMARY SCORE SHEET

Subject ID Number | Subject Initials | Visit Date: Day | Month | Year

PASAT Summary Score Sheet

FORM USED *(Check one)* ☐ Form A ☐ Form B

PASAT 3" Total Correct	Value	Range
		0-60

For a complete PASAT 3", record any circumstances that affect the patient's performance:

If PASAT 3" was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

PASAT 2" Total Correct	Value	Range
		0–60

For a complete PASAT 2", record any circumstances that affect the patient's performance:

If PASAT 2" was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Did it take more than one attempt to get one successful trial? ☐ Yes ☐ No

If yes, please specify reason(s) for more than one attempted trial:

Supplemental scores *(optional)*:

PASAT 3"		PASAT 2"	
Total correct in first half:	-------	Total correct in first half	-------
Total correct in second half:	-------	Total correct in second half:	-------
Total commission errors:	-------	Total commission errors:	-------
Total omission errors:	-------	Total omission errors:	-------

Instructions for carrying out the tests found in the original reference booklet.

13.2 Appendix 2 EDSS

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	- -
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	- - 2 0

SYNOPSIS OF FS SCORES

1. Visual[1]		5. Sensory	
2. Brainstem		6. Bowel/Bladder[1]	
3. Pyramidal		7. Cerebral	
4. Cerebellar			

[1] converted FS Score

EDSS Step

Signature

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity (corrected)		
Visual fields		

Scotoma	
* Disc pallor	
FUNCTIONAL SYSTEM SCORE	

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION	
Extraocular movements (EOM) impairment	
Nystagmus	
Trigeminal damage	
Facial weakness	

Hearing loss	
Dysarthria	
Dysphagia	
Other cranial nerve functions	
FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			

LIMB STRENGTH	R	L
Deltoids		
Biceps		
Triceps		
Wrist/finger flexors		
Wrist/finger extensors		
Hip flexors		

Knee flexors	
Knee extensors	
Plantar flexion (feet/toes)	
Dorsiflexion (feet/toes)	
* Position test UE, pronation	
* Position test UE, downward drift	
* Position test LE, sinking	
Able to lift only one leg at a time (grade in °)	° °
* Walking on heels	
* Walking on toes	
* Hopping on one foot	
SPASTICITY	
Arms	
Legs	
Gait	
FUNCTIONAL SYSTEM SCORE	

* = optional

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION		
Head tremor		
Truncal ataxia		
	R	L
Tremor/dysmetria UE		
Tremor/dysmetria LE		

Rapid alternating movements UE impairment		
Rapid alternating movements LE impairment		
Tandem walking		
Gait ataxia		
Romberg test		
Other, e. g. rebound		
FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L
Superficial sensation UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		

Position sense UE		
Position sense LE		
* Lhermitte's sign		
* Paraesthesiae UE		
* Paraesthesiae trunk		
* Paraesthesiae LE		
FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention		
Urinary urgency/incontinence		
Bladder catheterisation		

Bowel dysfunction	
* Sexual dysfunction	
FUNCTIONAL SYSTEM SCORE	

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION	
Depression	
Euphoria	

Decrease in mentation	
+ Fatigue	
FUNCTIONAL SYSTEM SCORE	

8. AMBULATION

Walking range as reported (without help or sticks)

meters	
in min	

Distance able to walk without rest or assistance	
≥ 100 meters, but < 200 meters	
≥ 200 meters, but < 300 meters	
≥ 300 meters, but < 500 meters	
≥ 500 meters but not unrestricted	
Unrestricted	
Actual distance (obligatory up to 500 m if possible)	
meters	

Requires **constant** assistance to walk 100 meters	
Unilateral assistance (in meters)	
Cane/crutch	
Other	
Bilateral assistance (in meters)	
Canes/crutches	
Other	
Assistance by another person (in meters)	

* = optional

+ Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52
©2007 Prof. L. Kappos, University Hospitals, Department of Neurology, CH-4031 Basel, Switzerland; Version 01/07

neurostatus scoring

Definitions for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52
©2007 Prof. L. Kappos, University Hospitals, Department of Neurology, CH-4031 Basel, Switzerland; Version 04/07

GENERAL GUIDELINES

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment.
Patients must be observed to walk the required distance.

NEUROSTATUS (NS)

In the Neurostatus, "signs only" is noted when the examination reveals signs of which the patient is unaware.

FUNCTIONAL SYSTEMS (FS)

A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS. Signs or symptoms that are not due to multiple sclerosis will not be taken into consideration for assessments, but should be noted.

UE = upper extremities
LE = lower extremities
* = optional

1 VISUAL (OPTIC) FUNCTIONS

VISUAL ACUITY

The visual acuity score is based on the line in the Snellen chart at 20 feet (5 meters) for which the patient makes no more than one error (use best available correction). Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations.

VISUAL FIELDS

0 normal
1 signs only: deficits present only on formal (confrontational) testing
2 moderate: patient aware of deficit, but incomplete hemianopsia on examination
3 marked: complete homonymous hemianopsia or equivalent

SCOTOMA

0 none
1 small: detectable only on formal (confrontational) testing
2 large: spontaneously reported by patient

* DISC PALLOR

0 not present
1 present

NOTE

When determining the EDSS step, the Visual FS score is converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1

FUNCTIONAL SYSTEM SCORE

0 normal
1 disc pallor and/or mild scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
2 worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 worse eye with large scotoma or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.2)
4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1); grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less
5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1); grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less
6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.3) or less

2 BRAINSTEM FUNCTIONS

EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT

0 none
1 signs only: subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort
2 mild: subtle and barely clinically detectable EOM weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware
3 moderate: obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye
4 marked: complete loss of movement in more than one direction of gaze in either eye

NYSTAGMUS

0 none
1 signs only or mild: gaze evoked nystagmus below the limits of "moderate" (equivalent to a Brainstem FS score of 1)
2 moderate: sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance
3 severe: sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

TRIGEMINAL DAMAGE

0 none
1 signs only
2 mild: clinically detectable numbness of which patient is aware
3 moderate: impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in the last 24 hours)
4 marked: unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

FACIAL WEAKNESS

0 none
1 signs only
2 mild: clinically detectable facial weakness of which patient is aware
3 moderate: incomplete facial palsy, such as weakness of eye closure that requires patching overnight or weakness of mouth closure that results in drooling
4 marked: complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

HEARING LOSS

0 none
1 signs only: hears finger rub less in one or both sides and has lateralized Weber test but does not complain of any hearing problem
2 mild: as in 1 but is aware of hearing problem
3 moderate: does not hear finger rub on one or both sides, misses several whispered numbers
4 marked: misses all or nearly all whispered numbers

DYSARTHRIA

0 none
1 signs only
2 mild: clinically detectable dysarthria of which patient is aware
3 moderate: obv. dysarthria during ordinary conversation that impairs comprehensibility
4 marked: incomprehensible speech
5 inability to speak

DYSPHAGIA

0 none
1 signs only
2 mild: difficulty with thin liquids
3 moderate: difficulty with liquids and solid food
4 marked: sustained difficulty with swallowing; requires a pureed diet
5 inability to swallow

OTHER CRANIAL NERVE FUNCTIONS

0 normal
1 signs only
2 mild disability: clinically detectable deficit of which patient is usually aware
3 moderate disability
4 marked disability

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only
2a moderate nystagmus
2b other mild disability
3a severe nystagmus
3b marked extraocular weakness
3c moderate disability of other cranial nerves
4a marked dysarthria
4b other marked disability.
5 inability to swallow or speak

3 PYRAMIDAL FUNCTIONS

REFLEXES

0 absent
1 diminished
2 normal
3 exaggerated
4 nonsustained clonus (a few beats of clonus)
5 sustained clonus

Cutaneous Reflexes

0 normal
1 weak
2 absent

***Palmomental Reflex**

0 absent
1 present

Plantar Response

0 flexor
1 neutral or equivocal
2 extensor

LIMB STRENGTH

The weakest muscle in each group defines the score for that muscle group. Use of functional tests, such as hopping on one foot and walking on heels/toes, are recommended in order to assess BMRC grades 3–5.

BMRC RATING SCALE

0 no muscle contraction detected
1 visible contraction without visible joint movement
2 visible movement only on the plane of gravity
3 active movement against gravity, but not against resistance
4 active movement against resistance, but not full strength
5 normal strength

FUNCTIONAL TESTS

***Pronator Drift (upper extremities) Pronation and downward drift:**

0 none
1 mild
2 evident

***Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:**

0 none
1 mild
2 evident
3 able to lift only one leg at a time (grade from the horizontal pos. at the hip joints...°)
4 unable to lift one leg at a time

***Walking on heels/toes**

0 normal
1 impaired
2 not possible

***Hopping on one foot**

0 normal
1 6–10 times
2 1–5 times
3 not possible

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

0 none
1 mild: barely increased muscle tone
2 moderate: moderately increased muscle tone that can be overcome and full range of motion is possible
3 severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible
4 contracted

GAIT SPASTICITY

0 none
1 barely perceptible
2 evident: minor interference with function
3 permanent shuffling: major interference with function

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 minimal disability: patient complains of fatigability or reduced performance in strenuous motor tasks and/or BMRC grade 4 in one or two muscle groups
3a mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups or BMRC grade 3 in one or two muscle groups; movements against gravity are possible
3b severe monoparesis: BMRC grade 2 or less in one muscle group
4a marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs
4b moderate tetraparesis: BMRC grade 3 in three or more limbs
4c monoplegia: BMRC grade 0 or 1 in one limb
5a paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs
5b hemiplegia
5c marked tetraparesis: BMRC grade 2 or less in three or more limbs
6 tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

4 CEREBELLAR FUNCTIONS

HEAD TREMOR

0 none
1 mild
2 moderate
3 severe

TRUNCAL ATAXIA

0 none
1 signs only
2 mild: swaying with eyes closed
3 moderate: swaying with eyes open
4 severe: unable to sit without assistance

LIMB ATAXIA (TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)

0 none
1 signs only
2 mild: tremor or clumsy movements easily seen, minor interference with function
3 moderate: tremor or clumsy movements interfere with function in all spheres
4 severe: most functions are very difficult

TANDEM (STRAIGHT LINE) WALKING

0 normal
1 impaired
2 not possible

GAIT ATAXIA

0 none
1 signs only
2 mild: abnormal balance only with tandem walking
3 moderate: abnormal balance with ordinary walking
4 severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another person because of ataxia

ROMBERG TEST

0 normal
1 mild: mild instability with eyes closed
2 moderate: not stable with eyes closed
3 severe: not stable with eyes open

OTHER CEREBELLAR TESTS

0 normal
1 mild abnormality
2 moderate abnormality
3 severe abnormality

NOTE

The presence of severe gait ataxia alone (without severe truncal ataxia and severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness on sensory deficits interfere with the testing of ataxia, score the patient's actual performance. To indicate the possible role of weakness make an "X" after the Cerebellar FS score.

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 mild ataxia
3a moderate truncal ataxia
3b moderate limb ataxia
3c moderate or severe gait ataxia
4 severe truncal ataxia and severe ataxia in three or four limbs
5 unable to perform coordinated movements due to ataxia
X pyramidal weakness (BMRC grade 3 or worse in limb strength) interferes with cerebellar testing

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

0 normal
1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 moderate: impaired discrimination of sharp/dull
4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 complete loss: anaesthesia

VIBRATION SENSE (AT THE MOST DISTAL JOINT)

0 normal
1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
3 marked: complete loss of vibration sense

POSITION SENSE

0 normal
1 mild: 1–2 incorrect responses, only distal joints affected
2 moderate: misses many movements of fingers or toes; proximal joints affected
3 marked: no perception of movement, astasia

***LHERMITTE'S SIGN**

Does not contribute to the Sensory FS score
0 negative
1 positive

***PARAESTHESIAE (TINGLING)**

Does not contribute to the Sensory FS score
0 none
1 present

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2a mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs
2b mild vibration or figure-writing or temperature decrease alone in three or four limbs
3a moderate decrease in touch or pain or position sense and/or essentially lost vibration in one or two limbs
3b mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4a marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs
4b moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5a loss (essentially) of sensation in one or two limbs
5b moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 sensation essentially lost below the head

6 BOWEL AND BLADDER FUNCTIONS

URINARY HESITANCY AND RETENTION

0 none
1 mild: no major impact on lifestyle
2 moderate: urinary retention; frequent urinary tract infections
3 severe: requires catheterisation
4 loss of function: overflow incontinence

URINARY URGENCY AND INCONTINENCE

0 none
1 mild: no major impact on lifestyle
2 moderate: rare incontinence occurring no more than once a week; must wear pads
3 severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads
4 loss of function: loss of bladder control

BLADDER CATHETERISATION

0 none
1 intermittent self-catheterisation
2 constant catheterisation

BOWEL DYSFUNCTION

0 none
1 mild: no incontinence, no major impact on lifestyle, mild constipation
2 moderate: must wear pads or alter lifestyle to be near lavatory
3 severe: in need of enemata or manual measures to evacuate bowels
4 complete loss of function

*SEXUAL DYSFUNCTION

Male

0 none
1 mild: difficulty to maintain erection during intercourse, but achieves erection and still has intercourse
2 moderate: difficulty to achieve erection, decrease in libido, still has intercourse and reaches orgasm
3 severe: marked decrease in libido, inability to achieve full erection, intercourse with difficulty and hypoorgasmia
4 loss of function

Female

0 none
1 mild: mild lack of lubrication, still sexually active and reaches orgasm
2 moderate: dysparunia, hypoorgasmia, decrease in sexual activity
3 severe: marked decrease in sexual activity, anorgasmia
4 loss of function

NOTE

When determining the EDSS step, the Bowel and Bladder FS score is converted to a lower score as follows:

Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild urinary hesitancy, urgency and/or constipation
2 moderate urinary hesitancy and/or urgency and/or rare urinary incontinence and/or severe constipation
3 frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowels
4 in need of almost constant catheterisation
5 loss of bladder or bowel function; external or indwelling catheter
6 loss of bowel and bladder function

7 CEREBRAL FUNCTIONS

DEPRESSION AND EUPHORIA

0 none
1 present: Patient complains of depression or is considered depressed or euphoric by the investigator or significant other.

DECREASE IN MENTATION

0 none
1 signs only: not apparent to patient and/or significant other
2 mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.
3 moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time
4 marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle
5 dementia, confusion and/or complete disorientation

+FATIGUE

0 none
1 mild: does not usually interfere with daily activities
2 moderate: interferes, but does not limit daily activities for more than 50 %
3 severe: significant limitation in daily activities (> 50 % reduction)

+ Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

NOTE

The presence of depression and/or euphoria alone results in a Cerebral FS score of 1a, but does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

FUNCTIONAL SYSTEM SCORE

0 normal
1a mood alteration (depression and/or euphoria) alone (does not affect EDSS step)
1b mild fatigue; signs only decrease in mentation
2 mild decrease in mentation; moderate or severe fatigue
3 moderate decrease in mentation
4 marked decrease in mentation
5 dementia

8 AMBULATION

DEFINITIONS

Observe the patient walking unassisted for a minimum distance of 500 meters, if possible. If the patient walks with assistance, observe the patient walking with the assistive device for a minimum distance of 130 meters, if possible.
If a patient walks without assistance and the walking range determines the EDSS step, please note that the definitions mark the lower limit for each step. For example, if a patient is able to walk 280 meters without aid or rest, the EDSS step is still 5.0. An EDSS step of 4.5 is defined by an unassisted walking distance of ≥300 meters (but <500 meters).
The definitions of EDSS steps 6.0 and 6.5 include both a description of the type of assistance required when walking and the walking range. In general, the type of assistance required (unilateral vs. bilateral) overrules the walking range when determining the EDSS step.

HOWEVER, THE FOLLOWING EXCEPTIONS APPLY:

1. If a patient is able to walk considerably longer than 100 meters (>120 meters) with two sticks, crutches or braces, the EDSS step is 6.0.
2. If a patient needs two sticks, crutches or braces to walk between 10 and 120 meters, the EDSS step is 6.5.
3. If a patient is able to walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.0.
4. If a patient cannot walk more than 50 meters with one stick, crutch or brace, the EDSS step is 6.5.

NOTE

1. Assistance by another person (as opposed to one stick, crutch or brace) is equivalent to bilateral assistance.
2. The use of an ankle foot orthotic device, without any other type of assistive device, is not considered unilateral assistance.

When determining the EDSS step, the Visual FS and Bowel and Bladder FS scores are converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1
Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Please enter both the actual and converted scores.

9 KURTZKE'S EXPANDED DISABILITY STATUS SCALE

DEFINITIONS

- EDSS steps below 4 refer to patients who are fully ambulatory (able to walk ≥500 meters). The precise step is defined by the Functional System (FS) scores.
- EDSS steps between 4.0 and 5.0 are defined by both the FS scores and the walking range. In general, the more severe parameter determines the EDSS step.
- EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.
- From steps 0 to 4.0, the EDSS should not change by 1.0 step, unless there is a similar change in a FS score by 1 grade.
- The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS.

NOTE

A Cerebral FS score of 1a due to depression and/or euphoria alone does not affect the EDSS step. However, a Cerebral FS score of 1b due to mild fatigue and/or signs only decrease in mentation contributes to the determination of the EDSS step.

EXPANDED DISABILITY STATUS SCALE

0 normal neurological exam (all FS grade 0)
1.0 no disability, minimal signs in one FS (one FS grade 1)
1.5 no disability, minimal signs in more than one FS (more than one FS grade 1)
2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1);or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0 ambulatory without aid or rest for ≥500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceecing limits of previous steps
4.5 ambulatory without aid or rest for ≥300 meters; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0 ambulatory without aid or rest for ≥200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5 ambulatory without aid or rest ≥100 meters
6.0 unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
7.0 unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 helpless bed patient; can communicate and eat
9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow
10 death due to MS

13.3 Appendix 3: Corticosteroids Side Effects

13.3.1 Side Effects

Fluid and Electrolyte Disturbances

Sodium retention; Congestive heart failure in susceptible patients; Hypertension; Fluid retention; Potassium loss-Hypokalemic alkalosis

MusculoskeletalMuscle weaknessLoss of muscle massSteroid

Myopathy;Osteoporosis;Tendon rupture, particularly of the Achilles tendon;Vertebral compression fractures;Aseptic necrosis of femoral and humeral heads;Pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage;Pancreatitis;Abdominal distentionUlcerative esophagitis,Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

Dermatologic

Impaired wound healing; Petechiae and ecchymosis; May suppress reactions to skin tests; Thin fragile skin; Facial erythema; Increased sweating

Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment; Convulsions; Vertigo; Headache

Endocrine

Development of Cushingoid state, Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness particularly in times of stress, as in trauma, surgery or illness; Menstrual irregularities; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus;Increased requirements of insulin or oral hypoglycemic agents in diabetics

Ophthalmic

Posterior sub capsular cataractsIncreased intraocular pressure; Glaucoma; Exophthalmos

Metabolic

Negative nitrogen balance due to protein catabolism.

The following additional reactions have been reported following oral as well as parenteral therapy: Urticaria and other allergic, anaphylactic or hypersensitivity reactions.

13.3.2 Warnings:

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.[1]These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.[2] There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior sub capsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers, who have received substantial doses of corticosteroids during pregnancy, should be carefully observed for signs of hypoadrenalism.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of MEDROL (methylprednisolone) Tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults, who have not had these diseases or been properly immunized against them, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyper infection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

13.3.3 PRECAUTIONS

General Precautions

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

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13.4 Appendix 4: UVADEX ® (methoxysalen) Label

UVADEX™ (methoxsalen)

Important Information

UVADEX® **Rx ONLY.**

(Methoxsalen)

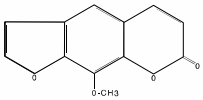
STERILE SOLUTION, 20 mcg/mL

Caution: Read the UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis System Operator's Manual prior to prescribing or dispensing this medication.

UVADEX® (methoxsalen) Sterile Solution should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience in the UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis System. Please consult the appropriate Operator's Manual before using this product.

DESCRIPTION

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the Ammi majus (Umbelliferae) plant. It belongs to a group of compounds known as psoralens or furocoumarins. The chemical name of methoxsalen is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one; it has the following structure:



Each mL of UVADEX® (methoxsalen, 8-methoxypsoralen) Sterile Solution contains methoxsalen 20 mcg, propylene glycol 50 mg, sodium chloride 8 mg, sodium acetate 1.75 mg, ethanol 0.05 mL, glacial acetic acid 0.0012 mL, and Water for Injection q.s. to 1.0 mL.

UVADEX® is used in combination with the UVAR™ XTS™ Photopheresis System to extracorporeally treat leukocyte enriched buffy coat.

CLINICAL PHARMACOLOGY

Mechanism of action: The exact mechanism of action of methoxsalen is not known. The best-known biochemical reaction of methoxsalen is with DNA. Methoxsalen, upon photoactivation, conjugates and forms covalent bonds with DNA which leads to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking of psoralen to both strands of DNA). Reactions with proteins have also been described.

For the palliative treatment of Cutaneous T-Cell Lymphoma, Photopheresis consists of removing a portion of the patient's blood and separating the red blood cells from the white cell layer (buffy coat) by centrifugation. The red cells are returned to the patient and the UVADEX® Sterile Solution is then injected into the instrument and mixed with the buffy coat. The instrument then irradiates this drug-cell mixture with ultraviolet light (UVA light, 320-400 nm) and returns the treated cells to the patient. See the appropriate Operator's Manual for details of this process. Although extracorporeal phototherapy exposes less than 10% of the total body burden of malignant cells to methoxsalen plus light, some patients achieve a complete response. Animal studies suggest that the photopheresis may activate an immune-mediated response against the malignant T-cells.

Use of the UVAR™ and UVAR™ XTS™ Systems after oral administration of methoxsalen were previously approved for the treatment of Cutaneous T-Cell Lymphoma. Interpatient variability in peak plasma concentration after an oral dose of methoxsalen ranges from 6 to 15 fold. UVADEX® is injected directly into the separated buffy coat in the instrument in an attempt to diminish this interpatient variability and to improve the exposure of the cells to the drug.

Methoxsalen is reversibly bound to serum albumin and is also preferentially taken up by epidermal cells. Methoxsalen is rapidly metabolized in humans, with approximately 95% of the drug excreted as metabolites in the urine within 24 hours.

Systemic administration of methoxsalen followed by UVA exposure leads to cell injury. The most obvious manifestation of this injury after skin exposure is delayed erythema, which may not begin for several hours and peaks at 48-72 hours. The inflammation is followed over several days to weeks, by repair which is manifested by increased melanization of the epidermis and thickening of the stratum corneum.

The total dose of methoxsalen delivered in UVADEX® is substantially lower (approximately 200 times) than that used with oral administration.

CLINICAL STUDIES

Three single-arm studies were performed to evaluate the effectiveness of photopheresis in the treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL). In the first study (CTCL 1), 39 patients were treated with the oral formulation of methoxsalen in conjunction with the UVAR™ Photopheresis System. The second study (CTCL 2) was a 5-year post approval follow-up of 57 CTCL patients that was conducted to evaluate long-term safety. This study also used the oral dosage formulation of methoxsalen. In the third study (CTCL 3), 51 patients were treated with the UVADEX® formulation of methoxsalen in conjunction with the UVAR™ Photopheresis System. In study CTCL 3, 86% of the patients were Caucasian, the median age was 62 years, and the average number of prior therapies was 4.3.

In study CTCL 1, prednisone up to 10 mg/day was permitted in addition to topical steroids. In CTCL 2, there was no concomitant medication restriction. In CTCL 3, topical steroids were permitted only for the treatment of fissures on the soles of the feet and the palms of hands. All other steroids, topical or systemic, were prohibited.

In all three studies, patients were initially treated on two consecutive days every four to five weeks. If the patient did not respond after four cycles, treatment was accelerated to two consecutive days every other week. If the patient did not respond after four cycles at the accelerated schedule, the patient was treated on two consecutive days every week. If the patient still did not respond after four cycles of weekly treatments, the schedule was increased to three consecutive days every week for three cycles. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment. Only two patients responded to treatment after six months. Clinical experience does not extend beyond this treatment frequency and there is no evidence to show that treatment with UVADEX® beyond six months or using a different schedule provided additional benefit.

Overall skin scores were used in the clinical studies of photopheresis to assess the patient's response to treatment. The patient's baseline skin score was used for comparison with subsequent scores. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy. Table 1 indicates the percent of successful responses within six months of beginning therapy for all patients who received at least one course of photopheresis. Only patients with patch plaque, extensive plaque and erythrodermic disease were enrolled in these studies. No patients with disease in the tumor phase were treated. There are no data available regarding the efficacy of UVADEX® in patients with disease in the tumor phase.

Table 1: Percentage of Successful Responses Within Six Months of Beginning Therapy

Study Response % Within Six Months
CTCL 3 (UVADEX™) 17/51 (33)
CTCL 2 (oral methoxsalen) 16/57 (28)
CTCL 1 (oral methoxsalen) 21/39 (54)

Although the response rate with UVADEX® in CTCL 3 was similar to with oral methoxsalen in CTCL 2, the possibility that UVADEX® is inferior in efficacy to oral methoxsalen cannot be excluded due to the design and size of the clinical trials. The higher response rate with oral methoxsalen in CTCL 1 may be partly due to patients receiving more treatments (mean of 64 in CTCL 1, 31 in CTCL 2, and 20 in CTCL 3), and to the administration of systemic steroids in CTCL 1.

Retrospective analyses of three clinical benefit parameters from the Body Area Severity Scores in CTCL 3 suggested a correlation between skin score response and improvement in edema, scaling and resolution of fissures.

INDICATIONS AND USAGE

UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis System in the palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL) that is unresponsive to other forms of treatment.

CONTRAINDICATIONS

PHOTOSENSITIVITY: UVADEX® (methoxsalen) Sterile Solution is contraindicated in patients exhibiting idiosyncratic reactions to psoralen compounds. Patients possessing a specific history of a light sensitive disease state should not initiate methoxsalen therapy. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum and albinism.

UVADEX® Sterile Solution is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses.

WARNINGS

Concomitant Therapy: Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents such as anthralin, coal tar or coal tar derivatives, griseofulvin, phenothiazines, nalidixic acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes such as methylene blue, toluidine blue, rose bengal and methyl orange.

Carcinogenicity, Mutagenesis, Impairment of Fertility: Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. In a prospective study of 1380 patients given PUVA therapy for psoriasis, 237 patients developed 1422 cutaneous squamous cell cancers. This observed incidence of cutaneous carcinoma is 17.6 times that expected for the general population. Previous cutaneous exposure to tar and UVB treatment, ionizing radiation or arsenic increased the risk of developing skin carcinomas after PUVA therapy. Because the dose of methoxsalen with UVADEX® therapy is about 200 times less than with PUVA and the skin is not exposed to high cumulative doses of UVA light, the risk of developing skin cancer following UVADEX® therapy may be lower.

Methoxsalen was carcinogenic in male rats that were given the drug by oral gavage five days per week for 103 weeks at doses of 37.5 and 75 mg/kg. The 37.5 mg/kg dose is about 1900 times greater than a single human methoxsalen dose during extracorporeal photopheresis treatment on a body surface area basis. The neoplastic lesions in rats included adenomas and adenocarcinomas of the tubular epithelium of the kidneys, carcinoma or squamous cell carcinoma of the Zymbal gland and alveolar or bronchiolar adenomas. Topical or intraperitoneal methoxsalen is a potent photo-carcinogen in albino mice and hairless mice.

With S9 activation, methoxsalen is mutagenic in the Ames test. In the absence of S9 activation and UV light, methoxsalen is clastogenic in vitro (sister chromatid exchange and chromosome aberrations in Chinese hamster ovary cells). Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair.

Pregnancy: Methoxsalen may cause fetal harm when given to a pregnant woman. Doses of 80 to 160 mg/kg/day given during organogenesis caused significant fetal toxicity in rats. The lowest of these doses, 80 mg/kg/day, is over 4000 times greater than a single dose of UVADEX® on a mg/m^2 basis. Fetal toxicity was associated with significant maternal weight loss, anorexia and increased relative liver weight. Signs of fetal toxicity included increased fetal mortality, increased resorptions, late fetal death, fewer fetuses per litter, and decreased fetal weight. Methoxsalen caused an increase in skeletal malformation and variations at doses of 80 mg/ kg/day and above. There are no adequate and well-controlled studies of methoxsalen in pregnant women. If UVADEX® is used during pregnancy, or if the patient becomes pregnant while receiving UVADEX®, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General: *ACTINIC DEGENERATION:*
After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin.

BASAL CELL CARCINOMAS:
Patients exhibiting multiple basal cell carcinomas or having a history of basal cell carcinomas should be diligently observed and treated.

SKIN BURNING:
Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions not followed.

THE FORMATION OF CATARACTS:
Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity. The concentration of methoxsalen in the human lens is proportional to the concentration in serum. Serum methoxsalen concentrations are substantially lower after extracorporeal UVADEX® treatment than after oral methoxsalen treatment. Nevertheless, if the lens is exposed to UVA light while methoxsalen is present, photoactivation of the drug may cause adducts to bind to biomolecules within the lens. If the lens is shielded from UVA light, the methoxsalen will diffuse out of the lens in about 24 hours.

Patients who use proper eye protection after PUVA therapy (oral methoxsalen) appear to have no increased risk of developing cataracts. The incidence of cataracts in these patients five years after their first treatment is about the same as that in the general population. Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after UVADEX® treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.

Information for Patients:
Patients should be told emphatically to wear UVA-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SP 15 or higher) for the twenty-four (24) hour period following treatment with methoxsalen, whether exposed to direct or indirect sunlight in the open or through a window glass.

Drug Interactions:
See **Warnings** Section.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
See **Warnings** Section.

Pregnancy:
Pregnancy Category D. See **Warnings** Section.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methoxsalen is administered to a nursing woman.

Pediatric Use:
Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenicity as described in the Warnings Section as well as the probability of actinic degeneration which is also described in the Warnings Section.

ADVERSE REACTIONS

Side effects of photopheresis (UVADEX® used with the THERAKOS™ Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%). In study CTCL 3 (UVADEX®), six serious cardiovascular adverse experiences were reported in five patients (5/51, 10%). Five of these six events were not related to photopheresis and did not interfere with the scheduled photopheresis treatments. One patient (1/51, 2%) with ischemic heart disease had an arrhythmia after the first day of photopheresis that was resolved the next day. Six infections were also reported in five patients. Two of the six events were Hickman catheter infections in one patient, which did not interrupt the scheduled photopheresis. The other four infections were not related to photopheresis and did not interfere with scheduled treatments.

OVERDOSAGE

There are no known reports of overdosage with extracorporeal administration of methoxsalen. However, in the event of overdosage, the patient should be kept in a darkened room for at least 24 hours.

DRUG DOSAGE AND ADMINISTRATION

Each UVADEX® treatment involves collection of leukocytes, photoactivation, and reinfusion of photoactivated cells. UVADEX® (methoxsalen) Sterile Solution is supplied in 10 mL vials containing 200 mcg of methoxsalen (concentration of 20 mcg/mL). The UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis System Operator's Manual should be consulted before using this product.

During treatment with the UVAR™ XTS™ or THERAKOS™ CELLEX™ Photopheresis System, the dosage of UVADEX® for each treatment will be calculated according to the treatment volume.

- The prescribed amount of UVADEX® should be injected into the recirculation bag prior to the Photactivation Phase using the formula:

  TREATMENT VOLUME X 0.017 = mL of UVADEX® for each treatment
  Example: Treatment volume of 240 mL X 0.017 = 4.1 mL of UVADEX®

Frequency/Schedule of Treatment: Normal Treatment Schedule:
Treatment is given on two consecutive days every four weeks for a minimum of seven treatment cycles (six months).

Accelerated Treatment Schedule:
If the assessment of the patient during the fourth treatment cycle (approximately three months) reveals an increased skin score from the baseline score, the frequency of treatment may be increased to two consecutive treatments every two weeks. If a 25% improvement in the skin score is attained after four consecutive weeks, the regular treatment schedule may resume. Patients who are maintained in the accelerated treatment schedule may receive a maximum of 20 cycles. There is no clinical evidence to show that treatment with UVADEX® beyond six months or using a different schedule provides additional benefit. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment and only two patients responded to treatment after six months.

HOW SUPPLIED

UVADEX® (methoxsalen) Sterile Solution 20 mcg/mL in 10 mL vials (NDC 64067-216-01), and cartons of 12 vials (NDC 64067-216-01). The drug product must be stored between 59°F (15°C) and 86°F (30°C).

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For Therakos, Inc., 1001 US Highway 202, Raritan, NJ 08869-0606 OG-866

13.5 Appendix 5: Therakos ® Cellex ® Photopheresis System

Details of the Therakos Photopheresis System can be found on this website:

http://www.therakos.com/healthcare-professionals/photopheresis