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UT Southwestern Medical Center
Clinical Center for Multiple Sclerosis

RISC™
RADIOLOGICALLY ISOLATED SYNDROME CONSORTIUM

Multi-center, randomized, double-blinded assessment of Tecfidera® in extending the time to a first attack in radiologically isolated syndrome (RIS) (ARISE)

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LIST OF ABBREVIATIONS

CSF	cerebrospinal fluid
CIU	core imaging unit
CCU	core clinical unit
EDSS	expanded disability status scale
EOS	end of study
IRB	institutional review board
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	multiple sclerosis functional composite
PI	principal investigator
PRO	patient reported outcomes
RIS	radiologically isolated syndrome

PROTOCOL SYNOPSIS

Title of study: Multi-center, randomized, double-blinded assessment of Tecfidera® in extending the time to a first attack in radiologically isolated syndrome (RIS) (ARISE)

Purpose: To prospectively study the efficacy of Tecfidera in extending the time to a seminal acute or progressive demyelinating event in a cohort of U.S. RIS subjects.

Rationale: RIS subjects are frequently exposed to disease modifying therapies despite the lack of scientific literature supporting the use of such treatments. Earlier treatment intervention may extend the time to the first acute or progressive clinical event resulting from CNS demyelination and reduce new radiological activity. In addition, early treatment may result in more profound effects on reducing disability progression long-term.

Primary outcome: The primary outcome measure for this trial is the time to the first acute or progressive neurological event resulting from CNS demyelination from randomization into the trial.

Population: This study will include RIS subjects from the U.S. who fulfill 2009 RIS Criteria[1].

Inclusion/Exclusion criteria:

Inclusion criteria

1. Males and females 18 years of age and older meeting 2009 RIS criteria[1]
2. Identified RIS cases with the initial MRI demonstrating anomalies suggestive of demyelinating disease dated ≥ 2009
3. Incidental anomalies identified on MRI of the brain or spinal cord with the primary reason for the acquired MRI resulting from an evaluation unrelated to multiple sclerosis
4. CNS white matter anomalies meeting the following MRI criteria:
    a. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
    b. T2-hyperintensities measuring > 3mm[2] and fulfilling 3 of 4 Barkhof-Tintoré criteria for dissemination in space
    c. CNS anomalies not consistent with a vascular pattern
    d. Qualitative determination that CNS anomalies have a characteristic appearance of demyelinating lesions
5. MRI anomalies do not account for clinically apparent neurological impairments in patients

Exclusion criteria

1. Women who are pregnant or nursing
2. Incomplete medical history or radiological data
3. History of remitting clinical symptoms consistent with multiple sclerosis lasting > 24 hours prior to CNS imaging revealing anomalies suggestive of multiple sclerosis
4. History of paroxysmal symptoms associated with MS (i.e. Lhermitte's or Uhthoff's phenomena)
5. CNS MRI anomalies are better accounted for by another disease process
6. The subject is unwilling or unable to comply with the requirements of the study protocol

7. Exposure to a disease modifying therapy for multiple sclerosis/RIS within the past 3 months
8. Exposure to high-dose glucocorticosteroid treatment within the past 30 days
9. Participation in other clinical trials involving treatment with a disease-modifying agent

Study design: Prospective, randomized, double-blinded, multi-center

Key data collection:

1. Clinical data
2. Radiologic data
3. Cognitive/Functional Assessments (EDSS, MSFC-expanded)
4. Patient reported surveys
5. Biological samples (CSF, serum DNA and RNA) for future mechanistic studies

Data analysis:

Primary analysis:

- We will evaluate the time from randomization to the first demyelinating event (acute or development of an initial symptom resulting in a progressive clinical course) utilizing Kaplan-Meier survival analyses. Log-rank tests will be used to compare survival data between groups at univariate analysis.

Secondary analyses:

- Multivariate Bayesian Cox regression models will be created to assess the independent predictive value of demographic characteristics (i.e. sex, ethnicity, age at the time of RIS diagnosis), clinical data (i.e. MS family history, occult neurological examination findings, environmental exposure data, cognitive performance, PRO, CSF profiles, etc.), and imaging data (i.e. number of brain MRI lesions, the presence of gadolinium enhancing lesions, geographical distribution of lesions, involvement of the spinal cord, brain atrophy, etc.) on the time to the first symptomatic event.

- The association of each covariate with time to the first clinical symptom will be quantified by hazard ratios (HR) along with their 95% confidence intervals (CI). Assessments to determine differences between centers will also be performed with statistical adjustments planned for subsequent analyses depending upon the obtained results.

- MRI outcomes (proportion of subjects with gadolinium enhancement and new radiologic activity).

ABOUT THIS STUDY

A strategic research alliance was formed between the Radiologically Isolated Syndrome Consortium (RISC) and Biogen to explore this important initiative of investigating the impact of early treatment intervention in subjects who possess the first visible manifestation of multiple sclerosis. This collaboration enabled the development and effective execution of an innovative approach in demyelinating disease more quickly and strategically. The current home of RISC, the University of Texas Southwestern Medical Center at Dallas (Texas, U.S.A.) is proud to serve as the study sponsor for this novel research study.

1. PURPOSE OF THIS MANUAL

This operations manual is a guide for participation in this clinical trial. All members of the study are responsible for following the procedures stipulated in this operations manual. Detailed

specifications and study procedures are provided for consistency in protocol adherence amongst participating clinics.

2. INTRODUCTION

2.1 Background

Multiple sclerosis (MS) is a common cause of severe neurological disability in young adults, resulting from an autoimmune interruption of both myelin and axons within the central nervous system (CNS). The diagnosis is made by fulfilling both spatial criteria, by meeting the requisite number of lesions within the brain or spinal cord, along with criteria for time, by demonstrating a history of at least a second clinical attack or the development of a new MS lesion on MRI after the seminal neurological event[2, 3]. Similar to many other chronic diseases, signs of impending disease may be observed in the months to years preceding the formal diagnosis. In the case of MS, healthy individuals who do not exhibit signs of neurological dysfunction commonly have brain MRI studies performed for a reason other than an evaluation for MS that reveal unexpected anomalies highly suggestive of demyelinating plaques given their size, location, and morphology[1, 4, 5]. These healthy subjects lack symptomatology suggestive of MS and fulfill formal criteria for radiologically isolated syndrome (RIS), a recently described MS subtype that expands upon the phenotype of at-risk individuals for future demyelinating events. A formal description of RIS was first introduced in 2009[1], to define this relevant cohort of individuals routinely encountered in clinical practice. The discovery of such anomalies creates intersecting neuro-ethical, legal, social, and practical medical management quandaries and is, therefore, of both immediate and long-term clinical significance. Despite advancements in the characterization of RIS subjects[6-9], and in our understanding of risk factors for initial symptom development[10, 11], the effect of treatment on such cases remain unclear. In addition, disease-modifying therapies are currently being recommended and prescribed outside of controlled clinical trial settings, placing subjects at risk for unnecessary exposure to both expensive and potentially harmful treatments.

2.2 Purpose & rationale

The purpose of this investigation is to systematically study the efficacy of Tecfidera in those individuals who possess incidental white matter anomalies within the brain following a MRI study that is performed for a reason other than for the evaluation of MS. A recent multi-national effort, involving RIS subjects from 5 countries, revealed that in 16% (73/451) of cases, regardless of the presence or absence of an asymptomatic spinal cord focus, a disease modifying therapy was prescribed prior to the development of a first clinical event[12]. Despite the intention by clinicians to prevent disease progression and the biological plausibility of altering the demyelinating course, there are no scientific data supporting the use of such treatments in RIS. The rationale for the proposed research is that earlier treatment intervention may extend the time to the first acute or progressive clinical event resulting from CNS demyelination and reduce new radiologic activity. In addition, exposure to earlier treatment compared to traditional treatment patterns in symptomatic groups may result in more profound effects on reducing disability progression long-term.

3. STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to assess the time from randomization to the first acute or initial neurological symptom resulting in a progressive clinical course related to CNS demyelination in those treated and untreated with Tecfidera.

Definitions:

Acute neurological event: The development of an acute neurological episode localized to the optic nerve, brainstem, cerebellum, spinal cord, or long sensory or motor tracts, lasting > 24 hours followed by a period of symptom improvement.

Progressive event: The onset of a clinical symptom (e.g. leg weakness) with the temporal profile revealing at least a 12-month progression of neurological deficits.

3.2 Secondary objectives
The secondary objectives of this study include the change in the number of new or enlarging T2 lesions, contrast enhancing lesions, T2-lesion volumes, and brain atrophy at End of Study.

3.3 Exploratory outcomes
Exploratory outcomes will include differences in cognitive performance and PRO between active treatment and placebo groups.

4. ORGANIZATION OF THE STUDY
4.1 Organizational Structure
The organizational structure of the clinical trial will consist of 15-20 clinical sites throughout the United States.

4.2 Clinical Centers
Each clinical center will be responsible for recruitment, treatment, evaluation of participants, and collection of study data according to the protocol. The Principal Investigator will direct each clinical center and each site will designate a study coordinator, manager, or regulatory specialist, where applicable. The roles and responsibilities of the study staff are described below. In addition, each center will consist of appropriate support personnel trained in human subject protection and HIPAA guidelines for research.

4.3 Principal Investigator (PI)
The Principal Investigator will be responsible for the overall conduct of research activities at the site, including:

- Conduct the study in accordance with the current protocol.
- Supervise the described investigation(s).
- Ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval are met.
- Submit all adverse experiences that occur in the course of the investigation via electronic data capture (EDC) for submission by the sponsor.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records and to make those records available for inspection.
- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
- Make no changes in the research without IRB approval except where necessary to eliminate apparent immediate hazards to human subjects.

4.4 Site Personnel: Clinical Research Project Manager, Regulatory & Contracts Specialist, & Study Nurse/Coordinator
A well-implemented protocol is often attributable to an organized, responsible study coordinator. The PI may delegate some or all of the following tasks to the study coordinator, regulatory specialist, and/or project manager. Under the PI's guidance, this person(s) may:

- Prepare regulatory documentation.
- Ensure the study is conducted in compliance with protocol requirements.
- Maintain IRB correspondence and regulatory documentation.
- Recruit potentially eligible subjects and evaluate them for protocol eligibility.
- Ensure that informed consent has been obtained from the participants before initiating any research-related activity.
- Schedule tests and appointments for participants within timeframes required by protocol.
- Complete Case Report Forms (CRFs) accurately.
- Collect data in accordance with the protocol.
- Maintain source documentation for each study participant in accordance with the protocol.
- Instruct and educate participants regarding study intervention modalities and anticipated side effects and their management.
- Monitor participant compliance.
- Identify and document adverse events and serious adverse events.
- Initiate Serious Adverse Event Reports (SAEs) and obtain the PI's signature within 24 hours, complete proper documentation notify proper individuals and fax report according to protocol.
- Identify and document protocol deviations.
- Respond to data queries in a timely manner.

5. STUDY PROCEDURES

5.1 Hypothesis

We hypothesize that treatment with Tecfidera will i) extend the time to the first acute or progressive demyelinating event by reducing CNS autoimmune inflammation and ii) reduce the development of new MRI lesions within the CNS compared to subjects randomized to placebo.

5.2 Central Clinical and Imaging Units

To accurately identify subjects with RIS, formal units will be created to review data prior to study entry.

5.2.1 Core Clinical Unit:

A Core Clinical Data Unit, led by Dr. Okuda, will be formed and comprised of a prominent international collaborator and trained MS specialist. This group will evaluate clinical information from both existing and new cases within partnering centers, including results from para-clinical studies (i.e. blood work, CSF, electrophysiological studies, etc.) to ensure that subjects accurately fulfill criteria for study entry. In addition, this group will be responsible for adjudicating all neurological events and post-attack clinical data during the study period. If a discrepancy exists between reviewers following the independent review of submitted cases, Dr. Okuda will provide a decision on the final classification. The Core Clinical Unit will unify all screening data (including conclusions from the Central Imaging Unit (below)) and will notify participating site PIs when entry criteria are met for potential study participants.

5.2.2 Central Imaging Unit:

A Central Imaging Unit will be formed and will be comprised of a board certified neuro-radiologist and MS specialist with neuro-imaging expertise. The MS specialist will confirm screened cases for study entry. MRI scans from subjects will be independently reviewed by the MS specialist and neuro-radiologist and determinations made if subjects fulfill MRI criteria for RIS. If a discrepancy exists between the two reviewers following the independent review of a case the MS specialist with neuro-imaging expertise will provide a decision on the final classification. The MS specialist with neuro-imaging expertise will also be responsible for

ensuring that a uniform protocol ("Dummy scans") is implemented at specified sites for the collection of uniform, multi-center data for post processing. In addition, this group will evaluate all MRI studies of the CNS for interval change (i.e. new and enlarging T2 lesion(s), gadolinium enhancement) during follow-up imaging studies and imaging studies acquired during clinical events. At End of Study, changes in T2-lesion volumes, and brain atrophy (SIENA) will be determined.

5.3 Study Design

This is a multi-center, randomized, double-blinded study in which approximately 90 RIS subjects (refer to section 12 for sample size justification) will be treated with either Tecfidera or placebo (1:1 randomization) for 3 years or until End of Study (EOS) which is March 31, 2021. The primary outcome measure is the time to the first acute or progressive neurological event resulting from CNS demyelination. The secondary outcome measures include the number of new or enlarging T2 lesions, and the change in the number of contrast enhancing lesions, and T2-lesion and brain volumes. Study participants, along with the treating and examining physicians, will be blinded to treatment assignment. Central Clinical and Imaging Units will screen all potential study subjects for inclusion/exclusion criteria. We expect to enroll all RIS subjects within the U.S.

Following informed consent and verification of entry criteria by the core units, study participants will be randomized 1:1 to either Tecfidera (120mg by mouth twice daily for 7 days with dose escalation to 240mg by mouth twice daily) or placebo. Clinical follow-up by the treating physician, as defined within this protocol, will occur at weeks **0, 48, 96, 144 and/or EOS** and during or immediately following clinical exacerbations. (please refer to Study Schematic). During clinical visits comprehensive medical history data, safety labs, and optional biological samples will be obtained by the treating physician.

Patients will be scheduled for safety screenings (CBC & CMP) at weeks **12, 24**, **72, 120**; at which time they will be seen by research coordinator or research nurse.

In addition to the face-to-face visits described above, study participants will be contacted over the telephone at weeks **4, 8, 36, 60, 84, 108, and 132** to assess for medical or treatment difficulties in addition to study medication compliance.

Standardized MRI studies of the brain will be performed at weeks 0 ,96, 144 or EOS; an additional MRI will be obtained at week 46 for those patients enrolled at the UTSW site only. Clinical imaging studies of the brain and/or spinal cord performed during or immediately following the onset of a clinical exacerbation will be performed at the discretion of the site PI with scan costs covered under the medical standard of care. A clinical MRI of the cervical spinal cord with and without contrast will be recommended to study participants at week 0 and week 144 as medical standard of care.

Participants who cannot receive contrast due to allergic reaction or abnormal blood counts will not be excluded from the study. Their imaging studies without contrast will be accepted.

All reported acute or progressive clinical events will be adjudicated by the Central Clinical Unit. Clinical visits due to suspected exacerbations associated with CNS demyelination, and associated diagnostic studies and treatments, will be covered under the medical standard of care by third party payers. A recommendation to re-evaluate the patient within 3 months following the clinical event to assess for extent of recovery will be made.

5.4 RIS subject numbering
Each RIS subject will be uniquely identified by a combination of the originating center and study subject number. Upon signing the informed consent, the subject will be given a unique participant number by the participating center PI. For example, the first RIS participant at UT Southwestern Medical Center (Dallas, Texas, U.S.A.) would be assigned the following identification number: UTSW-001.

5.5 Database fields
The following data will be captured in this study via electronic data capture (EDC).

Clinical Data: Comprehensive demographic data (i.e. date of birth, sex, race and ethnicity, etc.) and clinical data (i.e. date of first clinical visit, reason for the initial MRI scan, findings from the patient's clinical examination (*to include vital signs*), Visual Systems Tests (low vision contrast charts, ocular coherence tomography (OCT)) CMP and CBC results, cerebrospinal fluid test results, new onset clinical attacks, extent of recovery, etc. will be obtained from face-to-face clinical visits and existing medical records. Cognitive/Functional assessments (*EDSS, expanded MSFC (Timed 25-FT Walk (T25-FW), 9-Hole Peg Test (9-HPT), Paced Auditory Serial Addition Test (PASAT-3 (3-second interval pause)), Symbol Digit Modalities Test (SDMT*), will also be performed. Please refer to Appendix 1 – Cognitive/Functional Assessments

Patient Reported Surveys: Surveys containing questions related to Demographics, Family History, Lifestyle, Environment, and Environmental Exposure and the Neuro Quality of Life Questionnaire (*Neuro-QOL data*), will be completed by each study participant ; included will be inquiries into previous illnesses, the use of over-the-counter supplements, diet, occupational histories, exposure to vaccinations, etc. Please refer to Appendix 2 – Patient Reported Surveys.

Adverse events as well as concomitant medications will be collected and reported. All data collected for clinical assessments will be submitted via EDC and shared with Biogen. At the time of any patient withdrawing from the trial, an attempt will be made to determine the reason for discontinuation.

Radiological Data: Comprehensive radiological data will be collected from RIS subjects. Data to be incorporated into the study database include the date of the first MRI scan demonstrating anomalies within the brain that are suggestive of MS, number of lesions, lesion location, the presence of contrast enhancing lesions, the number of contrast enhancing lesions, changes observed between MRI studies, etc. In addition, data from the clinical MRI study of the cervical spine obtained at screening or Month 0 and at EOS will be incorporated if completed.

5.6 Detailed Patient Schedule of Assessments
Screening:
- Review of inclusion and exclusion criteria
- Evaluation of clinical and radiological data by the Core Clinical and Central Imaging Units
- Consent and Discussion of Study Expectations following approval for participation by the Centralized Units.

Week 0, +/- 2 weeks (approximately 2.5 hours)
- Record Demographics, and Medical and Clinical History
- Physical examination (including vital signs)
- Visual System tests (Low Vision Contrast charts, Ocular Coherence Tomography (OCT) (to be performed at UT Southwestern ONLY)
- Pregnancy test (urine)

- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
  - Spinal fluid (CSF) (optional)
- Standardized brain MRI at 1.5 or 3.0 Tesla
- Recommendation for MRI of the cervical spine with and without contrast (per medical standard of care)
- Obtain randomization number (1:1 Randomization of Tecfidera and Placebo)
- Administer Study Medication (including titration dosing)
- Review any adverse events and concomitant medications

Week 4, +/- 2 weeks (approximately 20 minutes)
- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications

Week 8, +/- 2 weeks (approximately 20 minutes)
- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications

Week 12, +/- 2 weeks: (approximately 20 minutes)
- Blood draw: CBC, CMP
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications
- Dispense Study Medication

Week 24, +/- 2 weeks: (approximately 20 minutes)
- Blood draw: CBC, CMP
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications
- Dispense Study Medication

Week 36, +/- 2 weeks: (approximately 20 minutes)
- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications
- Dispense Study Medication (via mail or patient pick up)

Week 48, +/- 2 weeks (approximately 1 hour):
- Review of Interval Medical History
- Physician examination (including vital signs)
- Visual System tests (Low Vision Contrast charts, Ocular Coherence Tomography (OCT) (to be performed at UT Southwestern ONLY)

- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
  - Spinal fluid (CSF) (optional)
- Standardized brain MRI at 1.5 or 3.0 Tesla (to be performed at UT Southwestern ONLY
- Dispense Study Medication
- Review any adverse events and concomitant medications

Week 60, +/- 2 weeks: (approximately 20 minutes)
- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Assessment of adverse events and changes in medications
- Dispense Study Medication (via mail or patient pick up)

Week 72, +/- 2 weeks, (approximately 20 minutes):
- Blood draw: CBC, CMP
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Dispense Study Medication
- Review any adverse events and changes in medications

Week 84, +/- 2 weeks: (approximately 20 minutes)
- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Dispense Study Medication (via mail or patient pick up)
- Review any adverse events and changes in medications

Week 96, +/- 2 weeks (approximately 2 hours):
- Review of Interval Medical History
- Physician examination (including vital signs)
- Visual System tests (Low Vision Contrast charts, Ocular Coherence Tomography (OCT) (to be performed at UT Southwestern ONLY)
- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
  - Spinal fluid (CSF) (optional)
- Standardized brain MRI at 1.5 or 3.0 Tesla
- Recommendation for MRI of the cervical spine with and without contrast (per medical standard of care)

- Dispense Study Medication
- Review any adverse events and concomitant medications

Week 108, +/- 2 weeks: (approximately 20 minutes)
- Telephone conversation

- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Review any adverse events and changes in medications
- Dispense Study Medication (via mail or patient pick up)

Week 120, +/- 2 weeks, (approximately 20 minutes):

- Blood draw: CBC, CMP
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Dispense Study Medication
- Review any adverse events and changes in medications

Week 132, +/- 2 weeks: (approximately 20 minutes)

- Telephone conversation
- Assessment for medical or medication difficulties
- Assessment of medication compliance
- Review any adverse events and changes in medications
- Dispense Study Medication (via mail or patient pick up)

Week 144, +/- 2 weeks (approximately 2 hours):

- Review of Interval Medical History
- Review of AEs and Concomitant Medications
- Physician examination (including vital signs)
- Visual System tests (Low Vision Contrast charts, Ocular Coherence Tomography (OCT) (to be performed at UT Southwestern ONLY)
- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
  - Spinal fluid (CSF) (optional)
- Standardized brain MRI at 1.5 or 3.0 Tesla
- Recommendation for MRI of the cervical spine with and without contrast (per medical standard of care)
- Collect all remaining study medication

Relapse Visit (approximately 2 hours):

- Review of Interval Medical History
- Review any adverse events and changes in medications
- Physician examination (including vital signs)
- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
- Recommendation for Standardized brain MRI at 1.5 or 3.0 Tesla at the discretion of the treating neurologist (per medical standard of care)

Unscheduled Visit (approximately 2 hours):

- Review of Interval Medical History
- Review any adverse events and changes in medications

- Physician examination (including vital signs)
- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- If standard of care brain CBC, CMP obtained at this visit, data should be recorded.
- If standard of care brain and/or cervical spine MRI completed at this visit, data should be recorded.

Early Withdrawal/Discontinuation or End of Study (approximately 2 hours):

- Review of Interval Medical History
- Review any adverse events and changes in medications
- Physician examination (including vital signs)
- Visual System tests (Low Vision Contrast charts, Ocular Coherence Tomography (OCT) (to be performed at UT Southwestern ONLY)
- Cognitive/Functional Assessments (Appendix 1)
- Patient Reported Surveys (Appendix 2)
- Blood draw: CBC, CMP
- Biological mechanistic samples for future use (including DNA/RNA),
  - Serum
  - Spinal fluid (CSF) (optional)
- Standardized brain MRI at 1.5 or 3.0 Tesla
- Recommendation for MRI of the cervical spine with and without contrast (per medical standard of care)
- Collect all remaining study medication

Table. Summary of study related events by visit.

Assessment	Screening	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
Informed Consent	X											
Review of Eligibility	X											
Evaluation by Clinical Core and Central Imaging	X											
Randomization		X										
Record History and Demographics		X						X				X
Visual Systems tests		UTSW only						UTSW only				UTSW only
Patient Reported Surveys		X						X				X
Physical Exam (including vital signs)		X						X				X
Cognitive/Functional Assessments		X						X				X
Pregnancy Test (urine)		X										
Blood draw : CBC/CMP for safety screening (local lab for PI review)		X			X	X		X		X		X
Biological sample for DNA/RNA: SERUM		X						X				X
CSF Samples (optional)		X						X				X
Medication Assessment & Dispense rx via pt pick up or mail		X			X	X	X	X	X	X	X	X
Brain MRI		X						UTSW only				X
Cervical Spine MRI (optional – standard of care)		SOC										SOC
Telephone conversation			X	X			X		X		X	
Patient Compensation		X						X				X
Review adverse events & changes in medication		X	X	X	X	X	X	X	X	X	X	X
Collect remaining study medication												

- SOC: If standard of care MRI completed at this visit, data should be recorded
- CBC & CMP (safety labs): To be processed on-site for PI review and NOT shipped to UTSW
- Medication Assessment & Administration INCLUDES completion of 'Drug Accountability Record'
- If subjects who were consented for 96 weeks choose not to extend their participation through week 114/or EOS, their week 96 should be recorded as 'early withdrawal' visit.

Assessment	Week 108	Week 120	Week 132	Week 144	Relapse	Early Withdrawal	Unscheduled
Informed Consent							
Review of Eligibility							
Evaluation by Clinical Core and Central Imaging							
Randomization							
Record History and Demographics				X	X	X	X
Visual Systems tests				UTSW only		UTSW only	
Patient Reported Surveys				X	X	X	X
Physical Exam (including vital signs)				X	X	X	X
Cognitive/Functional Assessments				X	X	X	X
Pregnancy Test (urine)							
Blood draw : CBC/CMP for safety screening (local lab for PI review)		X		X	X	X	SOC
Biological sample for DNA/RNA: SERUM				X	X	X	
CSF Samples (optional)				X		X	
Medication Assessment & Dispense rx via pt pick up or mail	X	X	X	X			
Brain MRI				X	SOC	X	SOC
Cervical Spine MRI (optional – standard of care)				SOC		SOC	SOC
Telephone conversation	X		X				
Patient Compensation				X			
Review adverse events & changes in medication					X	X	X
Collect remaining study medication				X		X	

5.7 Clinical exacerbations and radiological progression

All participating subjects will be advised to contact the lead site investigators if a clinical symptom is suspected or experienced in a RIS subject. Site PIs will be responsible for confirming clinical events and will perform the EDSS examination. Data will be entered via electronic data capture (EDC) for review by the Central Clinical Unit where the clinical exacerbation will be adjudicated. In the event of a suspected seminal acute or progressive demyelinating event, attempts will be made to evaluate the subject on an urgent basis within 48-72 hours from symptom onset by the site investigators (medical standard of care). Repeat imaging of the brain and spinal cord will be ordered at the discretion of the treating physician based on symptom localization and will be performed as per medical standard of care. Acute interventions (i.e. high-dose glucocorticosteroid treatment, etc.) will be prescribed and managed at the discretion of the treating physician at participating sites. The study visit will be labeled as either an “unscheduled visit” or a “relapse visit”. Study participant may be asked to provide additional biological specimens (serum) for future investigations. Sites will be encouraged to re-evaluate the patient within 3 months (medical standard of care) following the clinical event to assess the extent of recovery. All subjects who experience a seminal neurological event related to CNS demyelination, or those who are found to be intolerant to the study medication, will be provided with options highlighted in section 5.8.

RIS subjects will be made aware of any radiological progression identified on longitudinal imaging of the brain and spinal cord. As there is no FDA approved acute or long-term treatment for RIS, subjects will be extensively counseled by the PI as to their medical options.

5.8 Treatment options and safety monitoring following a confirmed relapse, intolerance to the study medication, or low absolute lymphocyte counts

5.8.1 When eligible, subjects on blinded study treatment who experience a confirmed clinical relapse by the Core Clinical Unit during the study will be offered the following options:

1. Remain on study treatment, with assignment remaining blinded
2. Prematurely discontinue blinded study treatment, begin treatment with Tecfidera (covered by Biogen up to 3-years from study enrollment date or until EOS) or subcutaneous peginterferon beta 1-a (Plegridy) if the study subject was randomized to Tecfidera, and remain in the study to complete a modified schedule of follow-up

   Modified Schedule of Follow-Up:

   - Re-evaluate patient within 3 mos of clinical event / relapse.

   - Patient then presents every 12 weeks for post-relapse (PR) follow up; Week 48 PR, Week 96 PR etc, until original EOS date.

3. Prematurely discontinue blinded study treatment, decline open-label treatment with Tecfidera or Plegridy, and remain in the study to complete the schedule of follow-up evaluations. Original treatment assignment remained blinded

5.8.2 Dose reduction treatment option for intolerable flushing and/or gastrointestinal disturbances related to study medication:

Patient-reported complaints of persistent, intolerable flushing and/or gastrointestinal disturbance to blinded study medication will be asked to reduce the blinded study medication administration to one capsule twice daily for one month. Following the one-month reduction in

dose, patients will be asked to resume taking two capsules twice daily. If the patient is still unable to tolerate the blinded study treatment, the patient will be required to discontinue study treatment.

Any patient continuing to experience intolerance to study medication following the one-month reduction in dose will be offered a switch to Plegridy as an alternative therapy. The patient will be unblinded to the study medication at this time. Plegridy will be administered per FDA-dosing and titration instructions for relapsing forms of multiple sclerosis.

Any patient continuing to experience intolerance to study medication following the one-month reduction in dose, refusing a switch in therapy to Plegridy, and prematurely discontinuing dosing with blinded study treatment due to intolerance will be asked to consider remaining in the study and encouraged to continue participation in the trial on a modified schedule of assessments. Patient treatment will remain blinded.

Modified Schedule of Follow-Up:

- Re-evaluate patient within 3 mos of clinical event / relapse.
- *Patient then presents every 12 weeks for post-relapse (PR) follow up; Week 48 PR, Week 96 PR etc, until original EOS date.*

5.8.3 Parameters for low lymphocyte counts:

In the event that the absolute lymphocyte count is observed to be <500 cells/L during any time within the study, a repeat blood draw will be performed 3 months later. If a sustained reduction of the absolute lymphocyte count is observed (<500 cells/L), the study subject will be unblinded to the study medication and removed from the randomized portion of the trial. Repeat assessments will be performed monthly until the absolute lymphocyte count is >500 cells/L. Once the absolute lymphocyte count is found to be >500 cells/L, study subjects randomized to Tecfidera will be given the opportunity to receive Plegridy (covered by Biogen until study conclusion).

The rationale for providing these options to subjects was 2-fold: to conduct this placebo-controlled study ethically and to make every effort to continue to follow the subjects (for efficacy and safety evaluations), even after they discontinued the study treatment.

5.8.4 Parameters for drug non-compliance

Patients who are non-compliant with medication dosing, or who discontinue taking their medication, may remain in the study in observation. They will remain on their original follow-up schedule but will no longer be dispensed medication. It should be noted in WebEz that medication has stopped.

6. SELECTION OF STUDY PARTICIPANTS

Inclusion criteria

1. Males and females 18 years of age and older meeting 2009 RIS criteria[1]
2. Identified RIS cases with the initial MRI demonstrating anomalies suggestive of demyelinating disease dated ≥ 2009
3. Incidental anomalies identified on MRI of the brain or spinal cord with the primary reason for the acquired MRI resulting from an evaluation of a process other than MS
4. CNS white matter anomalies meeting the following MRI criteria:
    a. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum

   b. T2-hyperintensities measuring > 3mm^2 and fulfilling 3 of 4 Barkhof-Tintoré criteria for dissemination in space
   c. CNS anomalies not consistent with a vascular pattern
   d. Qualitative determination that CNS anomalies have a characteristic appearance of demyelinating lesions
5. MRI anomalies do not account for clinically apparent neurological impairments in patients

Exclusion criteria

1. Women who are pregnant or nursing
2. Incomplete medical history or radiological data
3. History of remitting clinical symptoms consistent with multiple sclerosis lasting > 24 hours prior to CNS imaging revealing anomalies suggestive of MS
4. History of paroxysmal symptoms associated with MS (i.e. Lhermitte's or Uhthoff's phenomena)
5. CNS MRI anomalies are better accounted for by another disease process
6. The subject is unwilling or unable to comply with the requirements of the study protocol
7. Exposure to a disease modifying therapy for MS/RIS within the past 3 months
8. Exposure to high-dose glucocorticosteroid treatment within the past 30 days
9. Participation in other clinical trials involving treatment with a disease-modifying agent

7. STUDY MEDICATION

Study drug defined as Tecfidera or placebo will be provided at no cost to study participants. Study drug will be provided to the study sites by a study drug management vendor as triggered through an enrollment/randomization system. If patients are eligible to switch to Plegridy (due to study medication intolerance), this treatment will also be provided at no cost to the study participants for the duration of three 48ars from the date of randomization into the trial.

Any patient that becomes pregnant during the trial will discontinue study medication and complete the early withdrawal assessments according to the schedule of assessments table (page 14).

8. REPORTING ADVERSE EVENTS (AEs) AND SERIOUS ADVERSE EVENTS (SAEs)

8.1 Adverse Event Reporting

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that occurs after first dose of study treatment through week 144 or EOS visit or early withdrawal/discontinuation visit, whether or not considered related to study treatment. Signs and symptoms existing prior to first dose and documented on the baseline Medical History form or Physical Examination Form are not considered AEs. Only baseline signs and symptoms that worsen while the subject is on the study drug are considered adverse events.

At every visit, participant will be questioned regarding the occurrence and nature of any adverse experiences. If any signs, symptoms or the results of the laboratory tests indicate an adverse effect, the study physician should determine the severity (grade) of the AE and judge the relationship to the study treatment according to the current version of the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*. In addition, if an adverse event necessitates medical care, appropriate care will be provided. Adverse events should be documented on the Adverse Event Report form, regardless of relationship to the study drugs. Notably, AEs thought to be due to treatment with the study drug are still reported as AEs in this study. The following information will be collected for all Adverse

Events:

- Start and stop dates
- Severity (See the Severity Grading section below)
- CTCAE score
- Relationship to study drugs (See the Association with the Study Drug below)
- Action taken with study drugs
- Treatment for the AE and outcomes

Severity Grading

For evaluation and reporting purposes, events will be graded by a numerical score according to their impact on the subject's ability to perform daily activities as follows:

1 - Mild (causing no limitation of usual activities)
2 - Moderate (causing some limitation of usual activities)
3 - Severe (causing inability to carry out usual activities)

8.2 Association with the Study Drug

Association with the use of the study drug means that there is a reasonable possibility that the adverse event may have been caused by the drug under investigation. All adverse events are graded with regard to their association with the use of the study drug. The classifications used include Not Related or Related.

8.3 Serious Adverse Event (SAE)

A serious adverse event means any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, requires participant hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE, when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical / surgical intervention to prevent one of the outcomes listed above. Notably, any hospitalization, regardless of its nature, severity or etiology will be reported as an SAE. SAEs are collected from signing of Informed Consent through week 144 /or EOS visit or early withdrawal/discontinuation visit.

8.4 SAE Reporting Procedure

In the interest of subject safety and to fulfill regulatory requirements, all Serious Adverse Events, regardless of whether or not it is related to the study drug, should be reported to Quintiles Lifecycle Safety within 24 hours of event identification. Biogen or designee will forward a CIOMS form to the Sponsor-Principal Investigator to immediately onward submit to the FDA and all participating investigators in the study. All PIs are responsible for ensuring that all SAEs are recorded on the CRF and are reported to respective IRBs.

8.5 Withdrawal of Study Participants:

The researchers may decide to withdraw the patient from the study if:

- The medical problem becomes worse
- The researchers believe that participation in the research is no longer safe for the patient
- The researchers believe that other treatment may be more helpful
- The sponsor, IRB or the FDA stops the research for the safety of the participants
- The sponsor cancels the research
- The patient is unable to keep appointments or to follow the researcher's instructions

9. DATA SAFETY MONITORING BOARD (DSMB)

As Tecfidera is an approved FDA treatment for relapsing forms of multiple sclerosis, we do not anticipate any impediments to patient enrollment or significant adverse or serious adverse events. As a result, no data safety advisory board is required during the study.

10. INFORMED CONSENT

The informed consent form must be reviewed and approved by IRB. All revisions of the protocol must be reflected in the consent form and reviewed by the IRB. Obtaining informed consent is more than obtaining a signature on a form. It is a process designed to:

- Provide the participant with current and ongoing information about the study
- Ensure the participant understands the information that has been presented and has an opportunity to ask questions
- Discuss the participant's rights as outlined in the consent form
- Allow the participant the opportunity to agree or disagree to take part in the study, and
- Allow the participant the opportunity to freely withdraw from the study in the future. The investigator or coordinator should discuss in detail with the potentially eligible subjects about the nature, aims, duration, potential hazards of the study, and procedures to be performed during the study. The investigator or coordinator will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. The investigator must also explain that the participants are completely free to refuse to enter the study or to withdraw from it at any time. The written informed consent form should be signed and personally dated and timed by the participant. Participants receive a copy of the informed consent form. The original copy of the signed and dated consent form should be kept in the participant's source document file and a copy should be scanned into the patient's medical record. Subjects who refuse to participate should be treated without prejudice.
- Should be obtained prior to any study-related procedures

11. DATA REVIEW AND DATABASE MANAGEMENT Clinical and radiographic information will be transmitted to Core Clinical Unit via secure FTP – MOVEit DMZ.
Quintiles will provide for support related to data management, safety management, and project management. Data should be entered into eCRF (Oracle Inform) within 7 days of the visit, except: Day 1 data, which should be entered within 24 hours.
Automatic validation programs will be implemented by the external vendor to assess for data discrepancies. At the end of the study, each participating PI will certify that the data entered are complete and accurate prior to database lock.

12. DATA ANALYSIS

The purpose of this study is to assess the risk for a first clinical neurological event related to CNS demyelination in a cohort of RIS subjects from the U.S.

12.1 Power calculation

A Bayesian approach has been used to calculate the sample size. The Bayesian approach is based on combining a prior distribution for the treatment effect with the result of the trial (which represents here the likelihood). The prior distribution for the effect of Tecfidera vs. placebo was built using the data from DEFINE and CONFIRM trials in RRMS.

12.1.1 Parameter estimates for the rate of events in the RIS cohort in a Bayesian framework

The parameters for the expected treatment effect of a 50% reduction in the risk of the first clinical event are HR=0.50 (i.e. logHR=-0.69). A SD for logHR is set to 2.2 to get a power of 80% to detect a 50% reduction in the hazard of events with 80 patients per arm (original design). This base scenario is set in order to use the same assumptions done as for the original calculations.

Several scenarios were considered to allow a sensitivity analysis for the power calculations.

12.1.2 Parameters for the prior distribution – Scenario 1

The 2 arms treated with Tecfidera are pooled together (i.e. same efficacy)
Patients from DEFINE and CONFIRM are classified as “early RRMS” if they had:

- No previous treatment
- Less than 5 years from disease onset
- EDSS≤1.5

		Placebo	Tecfidera	Total
	RRMS	703	1372	2075
	Early	68	157	225
Total		771	1529	2300

225 patients are classified as Early in the 2 trials merged.

Treatment effect in the “Early” group (HR=0.24, risk reduction=76%) logHR=-1.45; SE=0.31.
Treatment effect in the rest of RRMS (HR=0.59, risk reduction 41%)

The parameters of the prior distribution, according to the Tecfidera effect in early RRMS in the DEFINE+CONFIRM studies, are: mean=-1.45, SD=0.31.

12.1.3 Parameters for the prior distribution – Scenario 2

The 2 arms treated with Tecfidera are pooled together (i.e. same efficacy)
We take the Tecfidera effect form the merged trials: HR=0.58, risk reduction=42%; logHR=-0.548; SE=0.073.

The parameters of the prior distribution, according to the Tecfidera effect all the patients included in the DEFINE+CONFIRM studies, are: mean=-0.548, SD=0.073.

12.1.4 Parameters for the prior distribution – Scenario 3

The 2 arms treated with Tecfidera are pooled together (i.e. same efficacy)
We take the Tecfidera effect form the merged trials: HR=0.58, risk reduction=42%
We assume the treatment effect on the RIS cohort to be reduced by 20% since there is a portion of RIS that are not subclinical MS.

HR=0.58*1.20 =0.70
logHR=-0.36
mean=-0.36, SD=0.073.

12.1.5 Parameters for the prior distribution – Scenario 4

The 2 arms treated with Tecfidera are pooled together (i.e. same efficacy)
We take the Tecfidera effect form the merged trials: HR=0.58, risk reduction=42%; SE=0.073

We assume the treatment effect on the RIS cohort to be reduced by 30% since there is a portion of RIS that are not subclinical MS.

HR=0.58*1.30 =0.75; logHR=-0.282; mean=-0.282, SD=0.073

We report here the different power estimates for a sample size of 80 RIS patients (40 per arm) according to the 4 scenarios and 4 different assumptions on SD (representing those observed multiplied by 2, 3, 4 and 5).

			SD			
	Prior HR	**Parameters for the prior**	**x2**	**x3**	**x4**	**x5**
Scenario 1 (early RRMS, subgroup of the trials)	**HR=0.235**	**Prior mu=-1.45, SD=0.31**	86%	70%	63%	9%
Scenario 2 (all RRMS in the trials)	**HR=0.58**	**Prior mu= -0.548, SD=0.07**	100%	99.60%	91.30%	80%
Scenario 3 (all RRMS with an effect diluted by 20%)	**HR=0.70**	**Prior mu= -0.362, SD=0.07**	99%	86%	70%	61%
Scenario 4 (all RRMS with an effect diluted by 30%)	**HR=0.75**	**Prior mu= -0.282, SD=0.07**	96%	67%	56%	49%

Overall, the power analysis shows that the projected sample size of 80 patients should result in adequate power for the majority of scenarios considered.

12.2. Patient demographic and other baseline characteristics

Patient demographic and baseline characteristic data will be described by means of absolute and relative frequencies for categorical variables and mean, standard deviation minimum and maximum, for continuous variables. Categorical variables will include sex, race, ethnicity, country, date of birth, age at RIS, etc.

12.3. Analysis of other variables

To validate the association between incidentally identified anomalies within the CNS that are highly suggestive of MS and seminal demyelinating events, systematically acquired environmental exposure, clinical, and radiological, data will be assimilated in an effort to identify significant risk factors. We will evaluate the time from the initial MRI revealing incidental anomalies to the first demyelinating event (acute or initial symptom resulting in a progressive clinical course) or new MRI focus utilizing Kaplan-Meier survival analyses. Log-rank tests will be used to compare survival data between groups at univariate analysis. Multivariate Bayesian Cox regression models will be created to assess the independent predictive value of demographic characteristics (i.e. sex, ethnicity, age at the time of RIS diagnosis), clinical data (i.e. MS family history, occult neurological examination findings, environmental exposure data, CSF profiles, cognitive performance, etc.), and imaging data (i.e. number of brain MRI lesions, the presence of gadolinium enhancing lesions, geographical distribution of lesions, involvement of the spinal

cord, brain atrophy, etc.) on the time to the first symptomatic event. The association of each covariate with time to the first clinical symptom will be quantified by hazard ratios (HR) along with their 95% confidence intervals (CI). Assessments to determine differences between centers will also be performed with statistical adjustments planned for subsequent analyses depending upon the obtained results. Corrections to co-variables will be made when necessary if baseline differences are detected.

13. TIMELINE ESTIMATE

- Contracting completion to IRB approval: 7 months
- Last patient in: September 30, 2019
- Last patient out: March 31, 2021
- Study completion and submission of final manuscript for publication: September 1, 2021

14. BIOMARKER ASSESSMENTS

Whole blood samples and cerebrospinal fluid (CSF) for biomarker analysis may be collected from all subjects and transferred to UT Southwestern biorepository. A portion of the biosamples will be stored at -80^{o}C prior to being shipped on dry ice to Biogen in batches every quarter where they will be centrally analyzed.

- Whole blood may be collected at week 0, week 48, week 96, week 144/or EOS,, Early Withdrawal and at relapse.
- CSF may be collected at week 0, week 48, week 96, and week 144/or EOS.

A total of approximately 400mL (25-27-30 tablespoons) of whole blood may be collected for the scheduled visits. Approximately 71 mL (5 tablespoons) of whole blood may be collected at each relapse or early withdrawal.

Those subjects who are unable or unwilling to contribute CSF samples will still be included in the study. Failure to acquire CSF will not be considered a protocol deviation.

The samples collected may be utilized to identify or verify putative prognostic and predictive markers associated with disease and markers of therapeutic response to DMF treatment. Baseline and dynamic (on-study) clinical disease characteristics and associated biomarker data may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to DMF treatment.

Specifically, whole blood, collected in EDTA coated and PAXgene tubes, and CSF, collected in PAXgene tubes, will be collected for future analysis of DNA, RNA, and protein biomarkers, as follows:

- Deoxyribonucleic acid (DNA) from whole blood collected at Baseline may be used for an exploratory pharmacogenomics analysis. Experience with treatment in MS shows that there is heterogeneity in clinical response, and some of the heterogeneity may be associated with genetic variants in patients. Genome-wide studies have identified approximately 50 single-nucleotide polymorphisms (SNPs) as MS-associated loci. DNA may be used for genome-wide or candidate gene SNP analysis. Allelic variants at SNP loci will be tested for association with efficacy and treatment response.
- Ribonucleic acid (RNA) from whole blood and CSF cell pellet may be used for analysis of gene expression. RNA may be used for genome-wide or candidate gene expression studies. The transcriptional profile will be used to understand the heterogeneity and to define the sub-structure of the MS patient population. Additionally, potential predictive

markers at Baseline through identification of transcript pattern that may predict disease/treatment outcome may be assessed.

- Serum and CSF samples may be used to determine the levels of markers of inflammation, pro- and anti-inflammatory cytokines related to T helper 1 (Th1)/Th2 and Th17 pathways, chemokines, and other proteins known to play a role in the transmigration of leukocytes and neurodegeneration. This targeted protein list is not all encompassing and may be expanded to include markers related to disease, efficacy or mechanism of action of DMF as more knowledge becomes available.
- In addition, serum and CSF samples will be stored for future exploratory analyses at UT Southwestern.

15. REFERENCES

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APPENDIX 1: Cognitive/Functional Assessments

EDSS, expanded MSFC (Timed 25-FT Walk (T25-FW), 9-Hole Peg Test (9-HPT), Paced Auditory Serial Addition Test (PASAT-3 (3-second interval pause)), Symbol Digit Modalities Test (SDMT)

- See attached

APPENDIX 2: Patient Reported Surveys

Surveys containing questions related to Demographics, Family History, Lifestyle, Environment, and Environmental Exposure and the Neuro Quality of Life Questionnaire (Neuro-QOL data), will be completed by each study participant ; included will be inquiries into previous illnesses,.

- See attached