Cover Page for Protocol, Statistical Plan and ICF

Official Title:	Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with secondary progressive forms of multiple sclerosis
NCT number:	NCT04925557
Document Type:	Study Protocol, Statistical Analysis Plan; Informed Consent Forms (Main)
Date of the Document:	Study Protocol: 3/3/2023 SAP: 9/15/2023 Consent Documents: 9/29/2022

PROTOCOL TITLE: Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with secondary progressive forms of multiple sclerosis

Local Supplement to Sponsor Protocol (HRP-508)

INSTRUCTIONS:

- *Only use this form when also providing a protocol (not just a grant application) from a sponsor or lead site (e.g. commercial, NIH, etc.). For all other protocols use HRP-503.*
- *Depending on the nature of your study, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable. For example, when accurate, the statement, "local inclusion criteria will not differ from those of the sponsor's protocol" could be provided in response to question 1.1.*
- *Provide the entire Sponsor protocol as a separate upload in Click IRB.*
- *Unless otherwise specified, provide only site-specific information below.*
- *When you write a single site supplement, keep an electronic copy. You will need to modify this copy when making changes. When you make changes, use the Track Changes feature.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it may not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Include the full protocol title.

Response: Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with active secondary progressive forms of multiple sclerosis

PROTOCOL TITLE: Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with secondary progressive forms of multiple sclerosis

PRINCIPAL INVESTIGATOR:

Name
Department
Telephone Number
Email Address

Response:

Robert Zivadinov
Neurology
716-859-7040
rzivadinov@bnac.net

FUNDING:

Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.

Response: Buffalo Neuroimaging Analysis Center

GRANT APPLICABILITY:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Response: Not applicable.

VERSION NUMBER/DATE:

Include the version number and date of this site supplement.

Response: 5, 03MAR23

Revision History

Revision #	Version Date	Summary of Changes	Consent Change?
1	24/06/2021	Change based on the new study protocol	Yes
2	28/02/22	Addition of Dent Institute as a recruitment and testing site	New MS consent for DENT; Yes to current MS consent form

3	07/04/2022	Inclusion of 15 healthy controls to undergo 1 PET scan and 1 MRI scan.	New HC consent form
4	11/9/2022	Including Great Lakes Medical Imaging as a PET scanning site	No
5	03/03/2023	Closing enrollment and follow-up of MS patients; Closure letter; continued enrollment of HCs	Yes - HC

Table of Contents

1.0 Study Summary

Study Title	Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with active secondary progressive forms of multiple sclerosis
Study Design	Open label, single-blinded, observation, prospective, longitudinal BNAC MRI analysts are blinded to subject's medication treatment.
Primary Objective	The assessment of the effect of Mayzent over at least 24 months on the evolution of microglia pathology in patients with active secondary-progressive (SP) MS.
Secondary Objective(s)	(a) compare the effect of Mayzent to the control group of active SPMS patients treated with ocrelizumab (Ocrevus®), as measured by changes in microglial activation in the lesional and non-lesional normal appearing (NA) WM and GM, and in the peri-plaque area of chronic lesions in the brain; (b) the relationship between changes in microglial activation in the lesional and non-lesional normal appearing

	(NA) WM and GM, and in the peri-plaque area of chronic lesions in the brain and clinical and behavioral outcomes. (b) to validate the quantification approach and to use as a statistical control group (15 HCs) when looking at an increase in TSPO in a parametric map of the brain
Research Intervention(s)/ Investigational Agent(s)	MRI and PET scans, clinical visits, questionnaires, eye exam, blood sampling.
IND/IDE #	
Study Population	Individuals with active Secondary Progressive Multiple Sclerosis (SPMS) Activity is determined by MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions) and/or clinical relapses in the 24 months prior to the study baseline. 15-age-matched healthy controls (10 females and 5 males aged between 18-65 years)
Sample Size	60 MS patients; 15 healthy controls
Study Duration for individual participants	2-3 years: MS Patients Approximately 4 hours: healthy controls – 1 timepoint
Study Specific Abbreviations/ Definitions	

AEs	Adverse Events
BBB	Blood-brain-barrier
BICAMS	Brief International Cognitive Assessment for MS
BNAC	Buffalo Neuroimaging Analysis Center
BVMT-R	Brief Visuospatial Memory Test – Revised
CE	Contrast Enhancing
CNS	Central Nervous System
CRFs	Clinical Research Forms
CSF	Cerebrospinal fluid
CVLT-II	California Verbal Memory Test – Second Edition
3-D	Three Dimensional
EDSS	Expanded Disability Status Scale
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ETL	Echo Train Length
FLAIR	Fluid-Attenuated Inversion Recovery
FLIRT	FMRIB's Linear Image Registration Tool

FMRIBs	Functional MRI of the Brain
FOV	Field of View
FSE	Fast Spin Echo
FSPGR	Fast Spoiled Gradient Echo
GFAP	Glial fibrillary acidic protein
GE	General Electric
GM	Gray Matter
GRE	Gradient Echo Sequence
HAB	High affinity for DNA polymorphism of the TSPO gene on chromosome 22q13.2 SNP
HD	High Definition
HDNV	Head and Neck Neurovascular Coil
HIPAA	Health Insurance Portability and Accountability Act
HIRES	High Resolution
IEC	Independent Ethics Committee
IR	Inversion Recovery
IRB	Investigational Review Board
IR-FSPGR	Inversion Recovery-Prepared fast Spoiled Gradient Recalled Sequence
ITT	Intention-to-Treat
LAB	Low affinity for DNA polymorphism of the TSPO gene on chromosome 22q13.2 SNP
LCLA	Low contrast letter acuity
LV	Lesion volume
MAB	Co-expression of LAB and HAB affinity for DNA polymorphism of the TSPO gene on chromosome 22q13.2 SNP
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTR	Magnetization transfer ratio
NA	Normal appearing
9-HPT	Nine-Hole Peg test
OCT	Optical coherence tomography
PBR	Peripheral benzodiazepine receptor
PBVC	Percent brain volume change
PCVC	Percent cortical volume change
PD	Proton Density
PET	Position emission tomography
PI	Prescribing information
PTVC	Percent thalamic volume change
RCP	Radiochemical purity
ROI	Region of interest
QSM	Quantitative susceptibility mapping
REB	Research Ethics Board

SAEs	Serious Adverse Events
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SE	Spin Echo
SIENA	Structural Image Evaluation, using Normalization of Atrophy
SIENAX	Structural Image Evaluation, using Normalization of Atrophy Cross-Sectional
sNfL	Serum neurofilament light chain
SNP	Single nucleotide polymorphism
SPGR	Spoiled Gradient Recalled Acquisition
SPMS	Secondary-progressive multiple sclerosis
SPSS	Statistical Package for the Social Sciences
TE	Echo Time
TI	Inversion Time
T25FW	Timed 25-Foot Walk
TR	Repetition Time
TSPO	18 kDa translocator protein
USPIO	Ultrasmall superparamagnetic iron oxide particles
VOI	Volume of interest
VT	Volume of distribution
VZV	Varicella zoster virus
WB	Whole Brain
WI	Weighted Image
WM	White Matter

2.0 Study Intervention/Investigational Agent

2.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response: The treatment provided to subjects is part of their routine clinical care as determined by their neurologist and the patients themselves. This project will not administer any drugs directly. The PET radiotracer will be produced directly on the morning before the scanning by the Canadian Molecular Probe Consortium ("CanProbe") in Toronto and transported to Buffalo. The contrast will be used during the PET scan

at the Center for Biomedical Imaging in accordance with EH&S *Radiation Safety* Program. The Ferumoxytol needed for research MRI scan will be kept in a locked cabinet in MRI suite available only to the investigators in the study.

Healthy controls will not be given a contrast agent during collection of the MRI scan.

2.2 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: IND application is approved for 18F-PBR06. The IND approval by FDA is under the code "IND 156679". The approval letter is included in the IRB submission.

3.0 Inclusion and Exclusion Criteria*

3.1 Describe any inclusion or exclusion criteria that will differ for your local site compared to the sponsor's protocol. For example, if the sponsor's protocol allows the enrollment of children but your site will not enroll children, indicate that here.

Response: This is a 1 site study (BNAC). Inclusion/exclusion criteria will be standard across any MS subjects to be enrolled. 15-age-matched healthy controls (10 females and 5 males aged between 18-65 years) will be enrolled.

4.0 Withdrawal of Subjects*

4.1 Describe procedures that will be followed locally, if different than the sponsor's protocol, when subjects withdraw from the research.

Response: Any premature withdrawal from the study will be recorded in the appropriate CRF. The person will be off study (no future assessments) and continue with standard of care as prescribed by his/her neurologist. If the subject discontinues the medication for medical reasons, every attempt will be made to complete the End of Treatment (EoT) testing schedule. The healthy control cohort is not being treated for any pathology related to a neurological disease.

5.0 Vulnerable Populations*

5.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response: Not applicable

6.0 Sharing of Results with Subjects*

6.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others

(e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response: In the event that an incidental finding is discovered on the MRI images, the individual's neurologist or primary care physician will be notified.

7.0 Setting

7.1 Describe the local sites or locations where your research team will conduct the research.

Response: For all participants, the MRI will take place at Buffalo General Hospital. The PET exam will take place at the CBI, located on the CTRC, 7th Floor or at Great Lakes Medical Imaging (GLMi) (**199 Park Club Lane, Suite 300, Williamsville)**.

For BNAC participants, clinical visits will take place at UBMD Neurology, located in the Conventus building at 1001 Main Street on the 4th floor.

7.2 Identify where your research team will identify and recruit potential subjects.

Response: MS subjects were referred by their neurologist. Healthy controls subjects will be recruited locally.

7.3 Identify where research procedures will be performed.

Response:

For all participants, the MRI will take place at Buffalo General Hospital. The PET exam will take place at the CBI, located on the CTRC, 7th Floor or at Great Lakes Medical Imaging (GLMi).

For BNAC participants, clinical visits will take place at UBMD Neurology, located in the Conventus building at 1001 Main Street on the 4th floor. For MS subjects, the clinical visit, demographic and MRI screen questionnaires will be administered at Buffalo General Hospital.

7.4 Describe the composition and involvement of any community advisory board.

Response: Not applicable.

7.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: Not applicable.

8.0 Resources Available

8.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not typically require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response: The clinicians are board certified neurologists and are considered experts in their field.

Clinical research unit (CRU) staff and Dent study team members– including project coordinators, clinical trial managers, and quality review associates – are certified in CITI and GCP. Staff within this unit are trained on all relevant SOPs and have access to all study-related documentation (e.g., protocol, scope of work, etc.). Additionally, CRU staff attend weekly teleconferences with the sponsor to ensure the staff is up-to-date on all study procedures and potential protocol deviations.

MRI analysis unit (MRIAU) staff – including analysts, physicists, and technical support – are certified in CITI and GCP. Staff within this unit are trained in all computer programs being utilized (JIM, Linux, etc.) and have an average of 7 years' experience in the field of MS brain analyses. Staff within this unit are trained on all relevant SOPs and have access to all study-related documentation (e.g., protocol, scope of work, etc.) and attend calibration meetings to ensure consistency among analysts.

PET and MRI staff are highly trained and certified to conduct these scans.

Describe other resources available to conduct the research: For example, as appropriate:

8.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: We plan to enroll 60 patients over an 18-month period. We believe this is quite feasible. Approximately 10 patients are prescribed Ocrevus and Mayzent in a month. (5 each) – *no longer applicable*

We also plan to enroll 15 healthy controls who are age and gender matched.

8.3 Describe the time that you will devote to conducting and completing the research.

Response: 60 months

8.4 Describe your facilities.

Response: BNAC is an MRI reading center located within Buffalo General Hospital; we are protected by both the hospital firewall and internal firewalls to prevent breach of data. DENT Neurologic Institute is the largest out-patient neurology practice in the United States. GLMI currently provides the radiology services for 6 hospitals and at 5 outpatient locations in and around Buffalo NY.

8.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response: Subjects will always have access to their neurologists or primary care physician.

8.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: The protocol will be shared with all personnel involved in recruiting, testing, and receiving, analyzing, and reporting on MRIs. BNAC has staff meetings to inform the appropriate personnel at the

beginning of each study and as necessary throughout the duration of the research.

9.0 Prior Approvals

9.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response: None.

10.0 Local Recruitment Methods

This section is for recruitment methods under the control of the local site and not central recruitment managed by the sponsor.

10.1 Describe when, where, and how potential subjects will be recruited.

Response: Subjects who were eligible to be prescribed Mayzent or Ocrevus by their neurologist while attending a clinical visit at UBMD Neurology at Conventus or the Dent Neurologic Institute. Healthy control subject will be recruited locally.

10.2 Describe the source of subjects.

Response: Patients who visit UBMD Neurology or Dent for management and treatment of SPMS. Healthy control subjects will be from other studies which they participated in and consented to be contacted for participation in future studies.

10.3 Describe the methods that will be used to identify potential subjects.

Response: Neurologists will assess their patients' eligibility to be prescribed either Mayzent or Ocrevus. All patients must be screened, per clinical protocols, to determine the safety of taking the prescribed medicine. *No longer applicable*

Healthy control subjects will be from other studies which they participated in and consented to be contacted for participation in future studies.

10.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: No materials; neurologist referrals.

Healthy control subjects will be from other studies which they participated in and consented to be contacted for participation in future studies.

10.5 Describe the amount and timing of any payments to subjects.

Response: Subjects will be paid by check for taking part in this study at each time point as it follows:

- If they complete the clinical visits, they will be paid $50
- If they complete a PET scan, they will be paid $100 per PET scan
- If they complete planned MRI scan over day one, they will be paid $50 and if they complete both MRIs over 2 days, they will be paid $100
- Healthy control subjects will be paid $250 after completion of the PET and MRI scans.

The total amount MS subjects may receive for taking part at every time point visit is $250. If the subject has to stop any procedure of the study visit early for any purpose, he/she will still receive compensation for his/her time, as above.

If MS subjects participate through all procedures in all five visits, they will be compensated in total of $1250.

- Healthy control subjects will be paid $250 after completion of the PET and MRI scans.

11.0 Local Number of Subjects

11.1 Indicate the total number of subjects to be accrued locally.

Response: 60 MS (*no longer applicable*); **15 HCs**

11.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects

needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

- Response: We estimate that 90 MS patients will need to be screened in order to achieve our enrollment goal of 60. *No longer applicable*
- Healthy control subjects will be from other studies which they participated in and consented to be contacted for participation in future studies.

12.0 Data Management and Confidentiality

Describe the local procedures for maintenance of confidentiality.

12.1 Where and how data or specimens will be stored locally?

Response: Electronic data will be stored on password-protected, dual-firewall encrypted machines in BNAC. Paper documentation is stored in locked cabinets in a locked room in the BNAC lab.

12.2 How long the data or specimens will be stored locally?

Response: MRIAU will have access to MRIs and ROI files. CRU will have access to paper and electronic clinical, cognitive and administrative documentation. The database management unit (DMU) will have access to the compiled data from our online repository.

12.3 Who will have access to the data or specimens locally?

Response: MRIAU will have access to MRIs and ROI files. CRU will have access to paper and electronic clinical, cognitive and administrative documentation. The database management unit (DMU) will have access to the compiled data from our online repository.

12.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response: UBMD and Dent neurologists are responsible for conducting and documenting the clinical visit. CRU is responsible for collecting the clinical data and associated testing data and receiving MRIs. The DMU is responsible for data entry and working with the PI on study-related database matters.

12.5 How data and specimens will be transported locally?

Response: Data is not transported to any external collaborators.

13.0 Provisions to Protect the Privacy Interests of Subjects

13.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response: Potential participants will meet with a full-time study coordinator in a private room where no one can overhear. The potential participants are provided all information regarding the full testing battery, length of participation, and reimbursement and reminded that their participation is entirely voluntary. At this time, participants are also able to ask additional questions regarding their participation.

13.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response: MS patients are very familiar with the tests being performed as part of this study. They are able to ask questions at any time. They can decline to answer any questions if they find them intrusive or uncomfortable. MRI, PET and lab assessments are only performed by licensed personnel. Tests are conducted in private settings.

Healthy control subjects will only undergo 1 MRI and 1 PET scan.

13.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response: Specifically, data is accessible only by those who have been assigned to the study and have the requisite training and experience. Each study personnel have their own logon ids and passwords to access the secure network drive at BNAC. Dent and Great Lakes Medical Imaging will not be housing any study related data. After collection, all study materials are given to BNAC.

14.0 Compensation for Research-Related Injury

14.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response:

Participants will receive medical treatment if they are injured or become ill as a result of this study. The doctor will explain the treatment options to them and tell them where they can get treatment.

The University at Buffalo and the Buffalo Neuroimaging Analysis Center (BNAC) makes no commitment to provide free medical care or payment for any unfavorable outcomes that result from their participation in this research. Medical services will be billed at the usual charge and will be the participant's responsibility or that of their third-party payer but the participants are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research including (BNAC) and the University at Buffalo."

14.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response: Not applicable.

15.0 Economic Burden to Subjects

15.1 Describe any costs that subjects may be responsible for because of participation in the research, e.g., fuel, parking, childcare.

Response: The subject does not have to pay for any of the procedures involved in this study.

16.0 Consent Process

16.1 Indicate whether you will be obtaining consent.

Response: Yes.

16.2 Describe where the consent process take place.

Response: Consenting will take place in a private room within BNAC UBMD Neurology, or *Dent (no longer applicable)*.

16.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response: When subjects are approached about participation in this study they can either choose to be consented and start the screening process at

that time, or they can contact a study coordinator at a later date of their choosing.

16.4 Describe any process to ensure ongoing consent.

Response: If there are any changes to the study procedures (*see study closure letter for patients*), subjects will be informed (possibly even asked to sign a new consent based on the change). The subjects are reminded that participation is voluntary and they are free to stop participating at any time without penalty or change to their clinical care.

16.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: ☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

16.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: Non-English speaking subjects will not be enrolled. The study is observational and does not offer any direct benefit.

16.7 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: This study has many questionnaires, all written in English. It is vital that study subjects are able to communicate with their neurologist regarding their medications and clinical care and that they are able to understand instructions when under-going MRI and PET scanning.

16.8 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response: Non-English speaking subjects will not be enrolled.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

16.9 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: We are not requesting a waiver of the consent process.

16.10 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have

provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: Not applicable.

Subjects who are not yet adults (infants, children, teenagers)

16.11 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response: Only adults aged 18-60 will be enrolled in this study.

16.12 For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: Research is only being conducted in NYS.

16.13 Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: Not applicable.

16.14 Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response: Not applicable.

16.15 Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response: Not applicable.

16.16 When assent of children is obtained describe whether and how it will be documented.

Response: Not applicable.

Cognitively Impaired Adults

16.17 Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response: We will not be enrolling cognitively impaired adults.

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment or decisional incapacity, a legally authorized representative must be used to provide consent and, where possible, assent of the individual should also be solicited.

16.18 List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for New York State.

Response: Only persons who are willing and able to provide informed consent will be enrolled in this study.

16.19 For research conducted outside of New York state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: This research will only take place in NYS.

16.20 Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects.* ***If some, indicate which subjects will be required to assent and which will not.***
- ***If assent will not be obtained from some or all subjects, an explanation of why not.***
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: Not applicable.

17.0 Process to Document Consent in Writing

17.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response: We will be following HRP-091.

18.0 Data and Specimen Banking*

18.1 The sponsor's protocol may require banking data or specimens for future use and both storage and use will be determined by the sponsor. If additional data or specimens will be banked locally for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.

Response: Data will be kept on site for the duration of the study and archived thereafter for the requisite 7 years. Hard copies will be locked in a separate, secure filing room open only to project coordinators and clinical trial managers. Electronic data will be kept on a password- and dual firewall-protected server available only to MRI analysts, physicists, technical-, and clinical-support staff.

18.2 List the data to be stored or associated with each specimen banked locally.

Response: MRI data with superimposed region of interest (ROI) files will be saved on the server. CRFs, clinical data and informed consent will all be kept and archived in BNAC. Data will be centrally managed by BNAC on a secure network. The network is password protected and can be accessed only by personnel as directed by the BNAC Director. Clinical data is stored in BNAC in coded charts that do not contain names, only study identifiers. All CRFs, MRI data, informed consent and other study data will be kept and archived in BNAC. The data will be quality controlled by BNAC and Jacobs MS Center staff. Information related to data will be treated in strict confidence to the extent provided by law.

18.3 Describe the procedures to release locally banked data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: A password-protected database will be sent to the sponsor at his/her written request. No data will otherwise be shared with any organization or entity.

Statistical Analysis Plan

"Open-label, single-blinded, comparative, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with active secondary progressive forms of multiple sclerosis"
2023-09-15

All statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA). The data distribution was determined using visual inspection of the histograms and Q-Q plots.

Categorical data was compared using chi-square test, parametric numerical data was compared using Student's t-test and non-parametric data using Mann Whitney U test. The comparisons between the groups were further adjusted for demographic and genetic differences using analysis of covariance (ANCOVA) and adjusted estimated means were shown as mean (standard error).

Due to the small sample size and non-parametric nature of the data, the correlations were performed using non-parametric Spearman's test. Pair-wise comparisons within the subjects were also performed. P-values lower than 0.05 were considered statistically significant. Due to the exploratory nature of the study, corrections for multiple comparisons were omitted. The data was additionally visualized using box and scatter plots.

MRI Analysis

Lesion activity:

The CE gadolinium and USPIO lesion number and lesion volume (LV) were measured on T1 post-contrast images, respectively, using a semi-automated edge detection contouring/thresholding technique previously described. Unenhanced T1 images were always used for comparison, and USPIO and gadolinium CE lesions were judged together as they would theoretically be in clinical situations. The cumulative number of CE gadolinium and USPIO lesions were obtained by summing the total number of these lesions between baseline to 6, 6 to 12, 12 to 24 months and 24 to 36 months.

The T2 new/enlarging lesions were assessed on FLAIR sequence. Using FMRIB's FLIRT, all follow-up FLAIR and T1-SE post-contrast images for a given subject were co-registered to its baseline FLAIR image using a 6 degrees-of-freedom rigid-body model. All subsequent lesion analyses were done using the co-registered images. For each time point, T2 lesion activity analysis was performed via the aid of a "subtraction image." Briefly, the image from the previous time point was subtracted from the corresponding current image. The result was then be smoothed with a Gaussian kernel of 0.5 mm. Cross-sectional regions of interest was overlaid on the subtraction image to facilitate the identification of new and enlarging T2 lesions. T2 and T1-LCs was calculated using JIM software (version 6.0, Xinapse Systems, Northants, UK, http://www.xinapse.com).

Brain volume analysis:
Segmentation of deep GM structures for volumetric and QSM analysis were done using both a semi-automated edge-contouring and FMRIB's integrated registration and segmentation tool (FIRST) on 3D T1-WI. Absolute tissue volumes for the thalamus and total subcortical deep GM at each time point were estimated from inpainted 3D T1-WI images with FMRIB's Integrated

Registration and Segmentation Tool, a model-based segmentation/registration tool. Normalized volumes were obtained by multiplying the estimated volumes from this tool by the volumetric scaling factor from SIENAX and percentage volume changes were obtained between different time points. Percent thalamus volume change (PTVC) was calculated.

For baseline analyses, FMRIB's SIENAX software was used (version 2.6) with inpainted 3D T1-WI. Normalized volumes were measured.

To quantify longitudinal percentage volume changes, we used a modified hybrid of FMRIB's SIENA and SIENAX methods. We used a brain- and skull-constrained co-registration technique to place both baseline and follow-up images into a joint space halfway between the two at all time points in the study. Next, we combined baseline and follow-up intracranial volume masks via union and valid voxel masks via intersection, ensuring that the same imaging volume was analyzed at both time points. Finally, we segmented the resulting images with a modified longitudinal version of FMRIB's Automated Segmentation Tool that uses a 4-dimensional joint hidden random Markov field to prevent misclassification between time points when longitudinal intensity changes are lacking (or minimal). Total tissue volume was calculated for both baseline and follow-up for each tissue compartment from partial volume maps and percentage volume change was derived directly from the images. Percentage brain volume change (PBVC) and percentage cortical volume change (PCVC) was calculated.

QSM analyses:

QSM images were reconstructed as previously described. Magnetic susceptibility was referenced (0 ppb) to the average susceptibility of the brain, under the assumption that a larger reference region would reduce additional inter-subject variability, compared to a smaller reference region. In-house developed algorithms for QSM processing, written in MATLAB (2013b, The MathWorks, Natick, MA) was used.

PET analysis:

Prior to regional analysis, subject-specific SUV maps were created. First, list-mode data was reconstructed into 5-minute frames and then aligned in order to correct for patient motion (see Figure 6 for further details). Next, aligned, decay-corrected activity maps were combined and then converted to voxel-wise standardized uptake value (SUV) maps (Figure 7) based on injected dose (ID) and body weight (BW) at the time of injection, using the formula $SUV=C_{img}/(ID/BW)$. To facilitate subsequent regional analysis, SUV maps were fused with MRI using the CT scan as an anatomical proxy.

For lesional and non-lesional NAWM and NAGM, and the peri-plaque area of chronic lesions in the brain analyses, the derived regions and/or expert-traced regions of interest (ROIs) from the fused MRI were applied to the PET scans to determine lesional and non-lesional ^{18}F-PBR06 binding. To correct for individual variation in tracer kinetics, SUV measures were referenced to the mean SUV of the cerebellum to produce relative SUVR measures for each relevant region of interest. Additionally, to correct for partial voluming of the larger PET voxels compared to MRI, region-based voxel-wise (RBV) correction combined with the reblurred Van-Cittert (RVC) was employed using PETPVC.

Permission to Take Part in a Human Research Study

University at Buffalo
The State University of New York

University at Buffalo Institutional Review Board (UBIRB)
Office of Research Compliance | Clinical and Translational Research Center Room 5018
875 Ellicott St. | Buffalo, NY 14203
UB Federalwide Assurance ID#: FWA00008824

Adult Consent to Participate in a Research Study as a Participant with Multiple Sclerosis for DENT participants.

Title of research study: **Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with secondary progressive forms of multiple sclerosis**

Version Date: ***28Feb22***

Investigator: Robert Zivadinov, MD, PhD

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?

You are being invited to take part in a research study because you have been diagnosed with a secondary progressive form of multiple sclerosis and will be starting treatment with either Mayzent or Ocrevus, as part of your clinical routine treatment.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this research is to examine the association between the development of microglia-related pathology using positron emission tomography (PET) and magnetic resonance imaging (MRI) in secondary progressive MS patients being treated with Mayzent or Ocrevus. Microglia is a type of cell found in the brain and spinal cord that is involved in the pathogenesis of multiple sclerosis (MS). Greater activation of these cells is related to development of secondary progressive MS, but it is unknown whether there is an effect of currently available MS treatments on these types of cells. Therefore, this research will use advanced imaging techniques to answer this important question using two commonly available, FDA approved, MS treatments.

How long will the research last and what will I need to do?

We expect that you will be in this research study for 5.5 hours at every time point, 3 years. There are 5 testing time points (baseline, 6 months, 12 months, 24 months and 36 months).

Permission to Take Part in a Human Research Study

Each testing point, you will be asked to have two MRI exams, a PET scan, and an Optical Coherence Tomography scan (OCT; eye exam). You will also be asked to complete a 25-foot walk, attend clinical visits with your neurologist and to complete questionnaires to ensure it is safe for you to have an MRI. An additional 4 questionnaires will evaluate your memory and mental processing. You will also have blood taken for laboratory examinations.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way being in this study could be bad for me?

Pregnant women will not be eligible to participate in this study.

During the MRI exam, you will be lying on your back. You may experience discomfort from lying still during the exam, or mild claustrophobia. To reduce discomfort, a cushion will be placed under your knees. Your head will be resting on a device called a head coil, which is necessary to collect the images. When images are being acquired, the MRI scanner produces continuous loud noise, which sounds like rapid hammering. You will be given ear plugs to help block out the sound of the MRI scanner. You may be offered headphones to listen to music during your scan. There is a microphone and a speaker in the MRI scanner, so you will be able to talk to the MRI technologist between scans. You will also be given a 'call ball' to hold in your hand during the exam that you can use if you urgently need to stop the exam.

During the PET scan, you will be exposed to radiation and during MRI of injection of gadolinium and Ferumoxytol. Please note that this radiation is not necessary for your medical care and is for research purposes only.

During the insertion of the IVs (MRI and PET) and blood draw you may experience a little pain at the site, some bruising and redness. Allergic reactions with the MRI contrast agent are very rare. However, there could be some itchy, redness at the injection site.

There are no known risks associated with the eye exam, clinical testing, physical, neurological, or cognitive assessments.

More detailed information about the risks of this study can be found under ***"Is there any way being in this study could be bad for me? (Detailed Risks)"***

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include better understanding of the interaction between cell components and other biological and clinical factors.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You may choose not to enroll in this study. Your alternative to participating in this research study is to not participate.

Permission to Take Part in a Human Research Study

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at rzivadinov@bnac.net (716-859-7040) or welmalik@dentinstitute.com (716-250-2000). You may also contact the research participant advocate at 716-888-4845 or researchadvocate@buffalo.edu.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (716) 888-4888 or email ub-irb@buffalo.edu

if:

- You have questions about your rights as a participant in this research
- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You want to get information or provide input about this research.

How many people will be studied?

We expect to recruit 60 people in this research study.

What happens if I say yes, I want to be in this research?

If you take part in this research, you will be asked to have two MRI exams, a PET scan, Optical Coherence Tomography (OCT; eye exam), and have physical and cognitive assessments. These tests are being conducted per the research protocol. Testing time points are 0 (baseline), and months 6, 12, 24, 36. For all participants, the MRI will take place at Buffalo General Hospital. The PET exam will take place at the Center for Biomedical Imaging, located on the Clinical Translational Research Center, 875 Ellicott St., Buffalo, 7th Floor. Clinical visits, OCT (eye exam) and study questionnaires will be administered at Dent.

Genotyping for the DNA polymorphism of the TSPO gene on chromosome 22q13.2 SNP:

All subjects will be genotyped for the DNA polymorphism of the TSPO gene on chromosome 22q13.2. This test allows us to determine the eligibility of each subject to proceed in the study. The information regarding these genes allows us to determine your ability to interface with the injected molecules. This procedure allows comparing subjects despite their different genetic background.

MRI (total of 10 scans for entire study; 2 scans at each time point)

The MRI will happen at Buffalo General Hospital on the 1st floor. The MRI will take approximately 2.5 hours over 2 days. The first day, you will perform an MRI scan similar to the one you usually obtain for the follow-up monitoring of your disease. Within the first approximately 45-50 minutes in the scanner, you will have a clinical routine MRI scan with use of gadolinium contrast agent administered through IV by a nurse. After the first 45-50 minutes of scanning with use of gadolinium contrast agent, you will start the research portion of the MRI scan which will utilize another injection of contrast agent known as Ferumoxytol. The injection will take about 15 minutes followed by 45 minutes of observational period. You will be observed for any signs or symptoms of an allergic reaction or intolerance to the contrast agent. That will conclude the first day of MRI scanning. You

will have the opportunity to take a 15 minute break after first 50 minutes of clinical routine scanning on the first day.

Because, it takes 24 hours for the Ferumoxytol contrast to become visible in the brain, in case of microglia activity, you will need to come on the next day to obtain a second MRI scan. When you come back the next day, you will be in the scanner only for approximately 15 minutes.

During the MRI procedure, you will be asked to lie on your back in the MRI machine. The MRI machine is a small tunnel into which you will be inserted. You will lie on your back and cannot move for the duration of testing. You will have a call button with which you can communicate with the technician performing the test. The MRI can produce loud knocking sounds. You can use ear plugs to reduce the noise if you wish.

PET (total of 5 visits for entire study)

The PET scanning is not performed in a clinical routine follow-up of MS patients. However, PET imaging is utilized in MS patients for research purposes. Therefore, the use of PET in this study will be done only for research purposes, to study microglia activation in the brain. During the research PET procedure, you will lie down on a padded table with your head in a special rest position so that you can stay still throughout the scan. You will then have an IV placed into your arm or hand in order to inject a tracer agent or dye typically used in routine PET scanning. During this procedure you will have 2 blood draws (about 4 teaspoons).. The whole PET session will last approximately 90 min. After you will be injected with the radiotracer, you will be observed for 45 min and then scanned for 45 minutes (between 45 to 90 minutes after injection). Additional 15 min will be used for position/removal of the patient in the injection room and PET/CT scanner. The scanner is very quiet. You can also listen to music or sleep during the scan. You will be asked to drink plenty of water before and after the scan to help flush the dye out of your system after scanning.

OCT (total of 5 visits for entire study)

This test will only take 5-10 minutes. We scan both of your eyes looking at the health of your eyes.

Low Contrast Letter Acuity (LCLA) has letters with varying sizes in different rows. You will be asked to read those letters. This test helps to measure your visual functioning.

Both tests are used for clinical routine follow-up purposes.

Clinical Visit (total of 5 visits for entire study)

You will see your neurologist for your physical and neurological assessments. These visits are routine in nature in that they should mimic your usual appointments that you have had with your neurologist in the past.

Health Questionnaires

You will be asked questions about your health status, medication use, and MS symptoms. This questionnaire is used for clinical routine follow-up purposes.

Health Screen Questionnaire

You will be asked questions about your overall health, education, and previous brain injuries. This questionnaire will take roughly 10 minutes to complete. This questionnaire is used for clinical routine follow-up purposes.

MRI Pre-Screen Questionnaire

Permission to Take Part in a Human Research Study

You will be asked questions about certain types of medical procedures and implants that may make it unsafe for you to complete an MRI. This questionnaire will take roughly 15 minutes to complete and is used for clinical routine follow-up purposes.

Contrast Screen

You will be asked a few questions about medications and any history of diabetes or kidney disease. Women of child bearing age will be asked about pregnancy.

Cognitive Questionnaires (no testing at the 6 month time point)

You will be asked to complete:

Symbol Digit Modalities Test (SDMT): This is a quick screen test for motor, visual and learning problems.

California Verbal Memory Test – Second Edition (CVLT-II): This test measures verbal learning and memory.

Brief Visuospatial Memory Test – Revised (BVMT-R): Tis test measures visuospacial learning and memory abilities.

The Auditory Test of Processing Speed (ATOPS): is a novel test being developed and piloted by the Benedict Lab to assess cognitive processing speed in individuals who may have severe motor or visual impairments. Patients are read a series of numbers and asked to answer simply "Yes" or "No" as to whether each number meets a pre-specified criteria.

At 12, 24, and 36 months we will ask you to complete a timed 25-feet walk (T25FW) test (testing lower extremity function) and the Nine-Hole Peg test (9-HPT) (testing upper extremity function).

Trained technicians will administer these questionnaires which take roughly 60 minutes to complete. These tests are used for clinical routine follow-up purposes.

A small amount of blood will be drawn (approximately 2 tablespoons). This will be used for research purpose of investigating experimental biomarkers related to microglia activity in the blood.

What are my responsibilities if I take part in this research?

We ask that you are honest in your responses during testing throughout the study. If you are uncomfortable with any question or procedure, you can stop and voluntarily stop participation with no penalty nor any change to your routine clinical care.

Women of child-bearing potential should adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

What happens if I say yes, but I change my mind later?

You can leave the research at any time. It will not be held against you.

Permission to Take Part in a Human Research Study

Is there any way being in this study could be bad for me? (Detailed Risks)

During the MRI exam, you will be lying on your back. You may experience discomfort from lying still during the exam, or mild claustrophobia. To reduce discomfort, a cushion will be placed under your knees. Your head will be resting on a device called a head coil, which is necessary to collect the images. When images are being acquired, the MRI scanner produces continuous loud noise, which sounds like rapid hammering. You will be given ear plugs to help block out the sound of the MRI scanner. You may be offered headphones to listen to music during your scan. There is a microphone and a speaker in the MRI scanner, so you will be able to talk to the MRI technologist between scans. You will also be given a 'call ball' to hold in your hand during the exam that you can use if you urgently need to stop the exam. The MRI has a potential, during normal use to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

The MRI scan uses a contrast agent called gadolinium to improve the image quality of the MRI. You will receive an intravenous injection of a contrast dye compound that is routinely used as part of standard MRI tests, but do have risks. During the placement of the IV, there may be pain from the needle or you may experience mild dizziness. A bruise where the needle was inserted could result after the IV is taken out. Gadolinium contrast is eliminated from the body by the kidneys, so a test of kidney function must be performed prior to participation in this study, and any patients with kidney problems will be excluded. In clinical trials, the most commonly reported adverse reactions to contrast in adults were headache and nausea. Less common reactions include vomiting, feeling hot, an allergic reaction at the injection site, distorted sense of taste, sensation of tingling, pricking or numbness, dizziness, rash or increased blood pressure. Some patients with severe or acute kidney impairment have developed a condition called nephrogenic systemic fibrosis (NSF) from receiving gadolinium contrast, a condition that may be fatal. You will be assessed for safety to receive this contrast agent. People with allergies, or known sensitivities to contrast agents similar to gadolinium are at increased risk for more serious side effects, and therefore will not be allowed to participate in this study. No toxic effects on the brain have been reported with repeated use of this type of contrast.

You will be also injected with another contrast agent called particle Ferumoxytol (Feraheme®). Risks of the intravenous injection include bleeding or bruising, and very rarely, infection. No higher risks of Ferumoxytol than gadolinium-based contrast agent have been reported. We will use slow infusion rather than bolus injection for this study. Although it has not been approved as a contrast agent for MRI, it has been extensively used in human MRI research. There are more than 820 publications related to its use since 2009 (when the agent was approved for human use). Ferumoxytol is safe in patients with chronic kidney disease since it is cleared from the circulation primarily by the reticuloendothelial system instead of the kidney. We will use a very low dose of Ferumoxytol (2.6 mg/kg for any given injection) in our human studies injected over 15 minutes. Our approach, using a low dose combined with a long injection time, is much safer than what is currently used. In rare instances, Ferumoxytol has been known to cause serious hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. In the clinical studies of Ferumoxytol, serious hypersensitivity reactions were reported in 0.2% (3/1726) of subjects receiving Ferumoxytol. Other adverse reactions potentially associated with hypersensitivity (e.g. pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1726) of these subjects.

As a result of your participation in this study you will be exposed to radiation from the PET scan. Please note that this radiation is not necessary for your medical care and is for research purposes only. The amount of radiation exposure you will receive from participation in this study is estimated to be

approximately 10 milliSieverts (mSv) or less over 18 months. A mSv is a unit of radiation dose. For comparison, everyone receives radiation exposure from natural background sources from the earth and the sky. The dose that you could receive from participation in this research study is about the same as you would normally receive in 3-4 years from these natural sources. Scientists disagree on whether radiation doses at these levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

If you are a woman who can become pregnant, you must have a negative blood pregnancy test before the research PET and MRI scan. Aside from the risk of radiation exposure, there are no known risks.

Putting in an IV catheter can cause pain, bleeding, or bruising at the place where the needle enters the vein. There is a very small risk of an infection or a bruise at the spot where we place the IV catheter. We will treat an infection with antibiotics. Bruises usually go away without treatment. You will feel a small pinch or have some bruising when you have the blood drawn.

There are no known risks associated with the clinical testing (walk, OCT, blood pressure, weight, etc.), physical, neurological, or cognitive assessments.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical or education records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization

Federal law provides additional protections of your medical records and related health information. These are described in the HIPAA section of this document.

If identifiers are removed from your identifiable private information, or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Can I be removed from the research without my OK?

The principal investigator of the study can remove you from the research study without your approval. Possible reasons for removal include an inability to complete the MRI or an indication that it would be unsafe for you to do so, or pregnancy. In order to ensure against pregnancy, participants are asked to use approved contraceptives for the duration of the study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

Who is paying for this research?

This research is being funded by Novartis, but is sponsored by the University at Buffalo.

What medical costs am I responsible for paying?

The tests or procedures required by the research study that would not otherwise be part of your standard care will be covered by the sponsor of this study. The tests or procedures that would be provided to any patient with your condition, regardless of whether he/she was participating in the

research study, are considered standard care and will be billed to you or your private or public health insurance company. You will still be responsible for the cost of your usual ongoing medical care, including deductibles and co-payments. If you have any questions about what expenses are covered by the sponsor and what expenses are the responsibility of you or your health insurance provider, please contact a member of the study staff and/or your health insurance provider.

Who will pay for my medical care if participating in this research harms me?

It is important that you tell your study doctor if you feel that taking part in this study has injured you or caused you to become ill.

You will receive medical treatment if you are injured or become ill as a result of this study. Your doctor will explain the treatment options to you and tell you where you can get treatment.

The University at Buffalo and the Buffalo Neuroimaging Analysis Center (BNAC) makes no commitment to provide free medical care or payment for any unfavorable outcomes that result from your participation in this research. Medical services will be billed at the usual charge and will be your responsibility or that of your third-party payer but you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research including (BNAC) and the University at Buffalo. The sponsor of the study is not providing subject injury coverage.

By accepting medical care or accepting payment for medical expenses, you are not waiving any of your legal rights.

Will I get paid for my participation in this research

If you agree to take part in this research study, we will pay you for your time and effort.

- If you complete the clinical visit, you will be paid $50
- If you complete a PET scan, you will be paid $100 per PET scan
- If you complete the planned MRI scan over day one, you will be paid $50 and if you complete both MRIs over 2 days, you will be paid $100

The total amount you may receive for taking part at every time point visit and completing the study is $1,250. You will be paid by check which will be mailed to you after each visit. If you have to stop any procedure of the study visit early for any purpose, you will still receive compensation for your time, as above. We will also pay UBER to transport you from home to testing and back for each MRI, PET and clinical visit.

Payments that you receive for your participation in this research are considered taxable income. If the amount of payment that you receive reaches or exceeds $600.00 in a calendar year, you will be issued a 1099 form.

What are my alternatives to participating in this research study?

Instead of being in this research study, you can choose to not participate.

What will happen to my information and samples?

Your information and samples (both identifiable and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

What will I be told about clinically relevant research results?

Permission to Take Part in a Human Research Study

Most tests done on samples in research studies are only for research purposes and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the PI of the study will notify your personal care physician who will contact you to let you know what we have found. If the researchers return genetic test results to you, it may be because they think you could have a health risk and want to recommend that the test should be re-done by a certified clinical laboratory to check the results. If this happens, then you may want to get a second test from a certified clinical laboratory, consult your own doctor, or get professional genetic counseling. You may have to pay for those additional services yourself.

HIPAA: Authorization for the Use and Disclosure of Identifiable Health Information for Research Purposes

This section describes information about you and about your health that will be obtained by the researchers when you participate in the research study. Health information is considered "protected health information" when it may directly identify you as an individual. By signing this form you are agreeing to permit the researchers and/or other parties (described in detail below) to have access to this information. If there are any parts of this form that you do not understand, please be sure to ask us for further clarification.

A. What protected health information will be collected about you as part of this research study?

X Information from your full medical records. This includes information related to the clinical, neurological, and/or physical evaluations for this study.
X New Health Information created from study related tests, procedures, visits, and/or questionnaires as described in this consent form.

B. Who is authorized to provide or collect this information?

X Principal Investigator or designee

C. With whom may your protected health information be shared?

Your health information may be shared with others outside of the research group for purposes directly related to the conduct of this research study or as required by law, including but not limited to:

X Clinical staff not involved in this research study who may become involved in your care if it is potentially relevant to your treatment
X The sponsor of this research study, Novartis, cooperative group, etc., or its agents
X The organization(s) responsible for administering this research: SUNY Buffalo's Research Foundation

Your information may also be shared with individuals or entities responsible for general administration, oversight and compliance of research activities. Examples of this include the institution's Privacy and Security Officers or other internal oversight staff, Safety Monitoring Boards, an Institutional Review Board, The Research Foundation of the State University of New York, University at Buffalo Foundation Services, and accrediting bodies, or with certain government oversight agencies that have authority over the research including the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the National

Institutes of Health (NIH), and the Office of Human Research Protections (OHRP). Your information may also be shared with other entities as permitted or required by law. All reasonable efforts will be used to protect the confidentiality of your individually identifiable health information that may be shared with others as described above.

All reasonable efforts will be used to protect the confidentiality of your protected health information. There is the potential for individually identifiable information and the associated health information obtained with this authorization to be re-disclosed by the recipient(s). After such a disclosure, the information may no longer be protected by the terms of this authorization against further re-disclosure.

D. How long will this information be kept by the Principal Investigator?

X a. This authorization has no expiration date. The researchers may continue to rely on this authorization to obtain and use protected health information about you unless you revoke this authorization in writing.

X d. Your protected health information will go into a database that will be maintained indefinitely. Any future study using this information that falls outside the scope of this current study will be required to follow guidelines designed to govern access to that information and to protect the privacy of that information.

Permission to Take Part in a Human Research Study

E. What are your rights after signing this authorization?

You have the right to revoke this authorization at any time. If you withdraw your authorization, no additional efforts to collect individually identifiable health information about you will be made. You should know, however, that protected health information acquired using this authorization prior to its withdrawal may continue to be used to the extent that the investigator(s) have already relied on your permission to conduct the research. If you chose to withdraw this authorization, you must do so in writing to the following individual(s):

Robert Zivadinov, MD
Department of Neurology
Buffalo Neuroimaging Analysis Center
D-2
100 High St., Buffalo, NY, 14203
716-859-7040

If you send us a request to withdraw your authorization, we will forward that request to the institutions we have shared it with in order to collect your individually identifiable health information.

F. What will happen if you decide not to sign this authorization?

Refusing to sign this authorization will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are otherwise entitled. If you decide not to sign this authorization, you will not be able to participate in the research study.

Permission to Take Part in a Human Research Study

Signature Block for Capable Adult

Your signature documents your permission to take part in this research. By signing this form you are not waiving any of your legal rights, including the right to seek compensation for injury related to negligence or misconduct of those involved in the research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Permission to Take Part in a Human Research Study

University at Buffalo
The State University of New York

University at Buffalo Institutional Review Board (UBIRB)
Office of Research Compliance | Clinical and Translational Research Center Room 5018
875 Ellicott St. | Buffalo, NY 14203
UB Federalwide Assurance ID#: FWA00008824

Adult Consent to Participate in a Research Study as a Healthy Participant

Title of research study: **Open-label, single-blinded, observational, prospective, 36-month, longitudinal, controlled study to assess the efficacy of siponimod (Mayzent®) on microglia in patients with secondary progressive forms of multiple sclerosis**

Version Date: ***30Sep22***

Investigator: Robert Zivadinov, MD, PhD

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?

You are being invited to take part in a research study because you are a healthy individual without multiple sclerosis (MS) or any other neurological disorders (OND).

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this research is to examine the association between the development of microglia-related pathology using positron emission tomography (PET) and magnetic resonance imaging (MRI) in secondary progressive MS patients being treated with Mayzent or Ocrevus. Microglia is a type of cell found in the brain and spinal cord that is involved in the pathogenesis of multiple sclerosis (MS). Greater activation of these cells is related to development of secondary progressive MS, but it is unknown whether there is an effect of currently available MS treatments on these types of cells. Therefore, this research will use advanced imaging techniques to answer this important question using two commonly available, FDA approved, MS treatments.

We are asking healthy controls to participate so that we can validate the choice of the reference region of the brain being studied in MS patients.

How long will the research last and what will I need to do?

We expect that you will be in this research study for about 4 hours.

Permission to Take Part in a Human Research Study

You will be asked to have one MRI exam, one PET scan, 1 physical exam and a demographic questionnaire. You will also be asked to complete a brief questionnaire to ensure it is safe for you to have an MRI.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way being in this study could be bad for me?

Pregnant women will not be eligible to participate in this study.

During the MRI exam, you will be lying on your back. You may experience discomfort from lying still during the exam, or mild claustrophobia. To reduce discomfort, a cushion will be placed under your knees. Your head will be resting on a device called a head coil, which is necessary to collect the images. When images are being acquired, the MRI scanner produces continuous loud noise, which sounds like rapid hammering. You will be given ear plugs to help block out the sound of the MRI scanner. You may be offered headphones to listen to music during your scan. There is a microphone and a speaker in the MRI scanner, so you will be able to talk to the MRI technologist between scans. You will also be given a 'call ball' to hold in your hand during the exam that you can use if you urgently need to stop the exam.

During the PET scan, you will be exposed to radiation and during MRI of injection of Ferumoxytol. Please note that this radiation is not necessary for your medical care and is for research purposes only.

During the insertion of the IVs (MRI and PET) you may experience a little pain at the site, some bruising and redness. Allergic reactions are very rare. However, there could be some itchy, redness at the injection site. You will not be given a contrast agent for the MRI.

There are no known risks associated with the physical or completion of the demographic questionnaire.

More detailed information about the risks of this study can be found under ***"Is there any way being in this study could be bad for me? (Detailed Risks)"***

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research. However, possible benefits to others include better understanding of the interaction between cell components and other biological and clinical factors.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You may choose not to enroll in this study. Your alternative to participating in this research study is to not participate.

Permission to Take Part in a Human Research Study

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at rzivadinov@bnac.net. You may also contact the research participant advocate at 716-888-4845 or researchadvocate@buffalo.edu.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). You may talk to them at (716) 888-4888 or email ub-irb@buffalo.edu

if:

- You have questions about your rights as a participant in this research
- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You want to get information or provide input about this research.

How many people will be studied?

We expect to recruit 15 healthy controls in this research study.

What happens if I say yes, I want to be in this research?

If you take part in this research, you will be asked to have one MRI exam and one PET scan.

Genotyping for the DNA polymorphism of the TSPO gene on chromosome 22q13.2 SNP:

All subjects will be genotyped for the DNA polymorphism of the TSPO gene on chromosome 22q13.2. This test allows us to determine the eligibility of each subject to proceed in the study. The information regarding these genes allows us to determine your ability to interface with the injected molecules. This procedure allows comparing subjects despite their different genetic background.

MRI

The MRI will happen at Buffalo General Hospital on the 1st floor. The duration of MRI is approximately 40 min and we will book additional 10 minutes for your positioning/removal into/from the scanner. Therefore, the total MRI protocol will be approximately of 50 min duration.

During the MRI procedure, you will be asked to lie on your back in the MRI machine. The MRI machine is a small tunnel into which you will be inserted. You will lie on your back and cannot move for the duration of testing. You will have a call button with which you can communicate with the technician performing the test. The MRI can produce loud knocking sounds. You can use ear plugs to reduce the noise if you wish.

PET

The use of PET in this study will be done only for research purposes, to study microglia activation in the brain. During the research PET procedure, you will lie down on a padded table with your head in a special rest position so that you can stay still throughout the scan. You will then have an IV placed into your arm or hand in order to inject a tracer agent or dye typically used in routine PET scanning. During this procedure you will have 2 blood draws (about 4 teaspoons). The whole PET session will last approximately 120 min. You will be given the opportunity to take a break for up to 15 minutes after 50 minutes of scanning, following which the last 60 minutes of scanning will be completed.

Permission to Take Part in a Human Research Study

The scanner is very quiet. You can also listen to music or sleep during the scan. You will be asked to drink plenty of water before and after the scan to help flush the dye out of your system after scanning.

MRI Pre-Screen Questionnaire

You will be asked questions about certain types of medical procedures and implants that may make it unsafe for you to complete an MRI. This questionnaire will take roughly 15 minutes to complete.

A small amount of blood will be drawn (approximately 2 tablespoons). This will be used for research purpose of investigating experimental biomarkers related to microglia activity in the blood.

Physical Examination: You will see a clinician for your physical assessments. This visit is routine in nature in that it should mimic your usual appointments that you would have with your primary care physician.

Demographic Questionnaire: There are a few questions regarding date of birth, gender, race, ethnicity and hand dominance.

What are my responsibilities if I take part in this research?

We ask that you are honest in your responses during testing throughout the study. If you are uncomfortable with any question or procedure, you can stop and voluntarily stop participation with no penalty nor any change to your routine clinical care.

What happens if I say yes, but I change my mind later?

You can leave the research at any time. It will not be held against you.

Is there any way being in this study could be bad for me? (Detailed Risks)

During the MRI exam, you will be lying on your back. You may experience discomfort from lying still during the exam, or mild claustrophobia. To reduce discomfort, a cushion will be placed under your knees. Your head will be resting on a device called a head coil, which is necessary to collect the images. When images are being acquired, the MRI scanner produces continuous loud noise, which sounds like rapid hammering. You will be given ear plugs to help block out the sound of the MRI scanner. You may be offered headphones to listen to music during your scan. There is a microphone and a speaker in the MRI scanner, so you will be able to talk to the MRI technologist between scans. You will also be given a 'call ball' to hold in your hand during the exam that you can use if you urgently need to stop the exam. The MRI has a potential, during normal use to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

As a result of your participation in this study you will be exposed to radiation from the PET scan. Please note that this radiation is not necessary for your medical care and is for research purposes only. The amount of radiation exposure you will receive from participation in this study is estimated to be approximately 10 milliSieverts (mSv) or less over 18 months. A mSv is a unit of radiation dose. For comparison, everyone receives radiation exposure from natural background sources from the earth and the sky. The dose that you could receive from participation in this research study is about the same as you would normally receive in 3-4 years from these natural sources. Scientists disagree on whether

radiation doses at these levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

You will be injected with a contrast agent called particle Ferumoxytol (Feraheme®). Risks of the intravenous injection include bleeding or bruising, and very rarely, infection. No higher risks of Ferumoxytol than gadolinium-based contrast agent have been reported. We will use slow infusion rather than bolus injection for this study. Although it has not been approved as a contrast agent for MRI, it has been extensively used in human MRI research. There are more than 820 publications related to its use since 2009 (when the agent was approved for human use). Ferumoxytol is safe in patients with chronic kidney disease since it is cleared from the circulation primarily by the reticuloendothelial system instead of the kidney. We will use a very low dose of Ferumoxytol (2.6 mg/kg for any given injection) in our human studies injected over 15 minutes. Our approach, using a low dose combined with a long injection time, is much safer than what is currently used. In rare instances, Ferumoxytol has been known to cause serious hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. In the clinical studies of Ferumoxytol, serious hypersensitivity reactions were reported in 0.2% (3/1726) of subjects receiving Ferumoxytol. Other adverse reactions potentially associated with hypersensitivity (e.g. pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1726) of these subjects.

If you are a woman who can become pregnant, you must have a negative blood pregnancy test before the research PET and MRI scan. Aside from the risk of radiation exposure, there are no known risks.

Putting in an IV catheter can cause pain, bleeding, or bruising at the place where the needle enters the vein. There is a very small risk of an infection or a bruise at the spot where we place the IV catheter. We will treat an infection with antibiotics. Bruises usually go away without treatment. You will feel a small pinch or have some bruising when you have the blood drawn.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical or education records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization

Federal law provides additional protections of your medical records and related health information. These are described in the HIPAA section of this document.

If identifiers are removed from your identifiable private information, or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Can I be removed from the research without my OK?

The principal investigator of the study can remove you from the research study without your approval. Possible reasons for removal include an inability to complete the MRI or an indication that it would be unsafe for you to do so, or pregnancy. In order to ensure against pregnancy, participants are asked to use approved contraceptives for the duration of the study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

Permission to Take Part in a Human Research Study

What else do I need to know?

Who is paying for this research?

This research is being funded by Novartis, but is sponsored by the University at Buffalo.

What medical costs am I responsible for paying?

The tests or procedures required by the research study that would not otherwise be part of your standard care will be covered by the sponsor of this study. You will still be responsible for the cost of your usual ongoing medical care, including deductibles and co-payments. If you have any questions about what expenses are covered by the sponsor and what expenses are the responsibility of you or your health insurance provider, please contact a member of the study staff and/or your health insurance provider.

Who will pay for my medical care if participating in this research harms me?

It is important that you tell the study team if you feel that taking part in this study has injured you or caused you to become ill.

You will receive medical treatment if you are injured or become ill as a result of this study. Your doctor will explain the treatment options to you and tell you where you can get treatment.

The University at Buffalo and the Buffalo Neuroimaging Analysis Center (BNAC) makes no commitment to provide free medical care or payment for any unfavorable outcomes that result from your participation in this research. Medical services will be billed at the usual charge and will be your responsibility or that of your third-party payer but you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research including (BNAC) and the University at Buffalo. The sponsor of the study is not providing subject injury coverage.

By accepting medical care or accepting payment for medical expenses, you are not waiving any of your legal rights.

Will I get paid for my participation in this research

If you agree to take part in this research study, we will pay you for your time and effort.

You will be compensated $250 for completion of the MRI, PET and physical exams and completion of the questionnaires.

You will be paid by check which will be mailed to you after each visit. If you have to stop any procedure of the study visit early for any purpose, you will still receive compensation for your time, as above. We will also pay UBER to transport you from home to testing for the MRI and PET exams.

Payments that you receive for your participation in this research are considered taxable income. If the amount of payment that you receive reaches or exceeds $600.00 in a calendar year, you will be issued a 1099 form.

What are my alternatives to participating in this research study?

Instead of being in this research study, you can choose to not participate.

What will happen to my information and samples?

Your information and samples (both identifiable and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

What will I be told about clinically relevant research results?

Most tests done on samples in research studies are only for research purposes and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the PI of the study will notify your personal care physician who will contact you to let you know what we have found. If the researchers return genetic test results to you, it may be because they think you could have a health risk and want to recommend that the test should be re-done by a certified clinical laboratory to check the results. If this happens, then you may want to get a second test from a certified clinical laboratory, consult your own doctor, or get professional genetic counseling. You may have to pay for those additional services yourself.

HIPAA: Authorization for the Use and Disclosure of Identifiable Health Information for Research Purposes

This section describes information about you and about your health that will be obtained by the researchers when you participate in the research study. Health information is considered "protected health information" when it may directly identify you as an individual. By signing this form you are agreeing to permit the researchers and/or other parties (described in detail below) to have access to this information. If there are any parts of this form that you do not understand, please be sure to ask us for further clarification.

A. What protected health information will be collected about you as part of this research study?

X Name, gender, date of birth
X New Health Information created from study related tests, procedures, visits, and/or questionnaires as described in this consent form.

B. Who is authorized to provide or collect this information?

X Principal Investigator or designee

C. With whom may your protected health information be shared?

Your health information may be shared with others outside of the research group for purposes directly related to the conduct of this research study or as required by law, including but not limited to:

X Clinical staff not involved in this research study who may become involved in your care if it is potentially relevant to your treatment
X The sponsor of this research study, Novartis, cooperative group, etc., or its agents
X The organization(s) responsible for administering this research: SUNY Buffalo's Research Foundation

Your information may also be shared with individuals or entities responsible for general administration, oversight and compliance of research activities. Examples of this include the institution's Privacy and Security Officers or other internal oversight staff, Safety Monitoring

Boards, an Institutional Review Board, The Research Foundation of the State University of New York, University at Buffalo Foundation Services, and accrediting bodies, or with certain government oversight agencies that have authority over the research including the Department of Health and Human Services (HHS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of Human Research Protections (OHRP). Your information may also be shared with other entities as permitted or required by law. All reasonable efforts will be used to protect the confidentiality of your individually identifiable health information that may be shared with others as described above.

All reasonable efforts will be used to protect the confidentiality of your protected health information. There is the potential for individually identifiable information and the associated health information obtained with this authorization to be re-disclosed by the recipient(s). After such a disclosure, the information may no longer be protected by the terms of this authorization against further re-disclosure.

D. How long will this information be kept by the Principal Investigator?

X a. This authorization has no expiration date. The researchers may continue to rely on this authorization to obtain and use protected health information about you unless you revoke this authorization in writing.

X d. Your protected health information will go into a database that will be maintained indefinitely. Any future study using this information that falls outside the scope of this current study will be required to follow guidelines designed to govern access to that information and to protect the privacy of that information.

Permission to Take Part in a Human Research Study

E. What are your rights after signing this authorization?

You have the right to revoke this authorization at any time. If you withdraw your authorization, no additional efforts to collect individually identifiable health information about you will be made. You should know, however, that protected health information acquired using this authorization prior to its withdrawal may continue to be used to the extent that the investigator(s) have already relied on your permission to conduct the research. If you chose to withdraw this authorization, you must do so in writing to the following individual(s):

Robert Zivadinov, MD
Department of Neurology
Buffalo Neuroimaging Analysis Center
D-2
100 High St., Buffalo, NY, 14203
716-859-7040

If you send us a request to withdraw your authorization, we will forward that request to the institutions we have shared it with in order to collect your individually identifiable health information.

F. What will happen if you decide not to sign this authorization?

Refusing to sign this authorization will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are otherwise entitled. If you decide not to sign this authorization, you will not be able to participate in the research study.

Permission to Take Part in a Human Research Study

Signature Block for Capable Adult

Your signature documents your permission to take part in this research. By signing this form you are not waiving any of your legal rights, including the right to seek compensation for injury related to negligence or misconduct of those involved in the research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	