Prospective Evaluation of Sequencing from antiCD-20 Therapies to Ozanimod

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Background

Multiple sclerosis (MS) is a complex autoimmune disorder of the central nervous system. This condition affects nearly 1 million patients in the United States(1). A unique aspect of this condition is that relapses occur more frequently at the beginning of the illness as demonstrated by natural history studies(2, 3). This suggests that starting with a high efficacy approach followed by de-escalation in treatment may be ideal especially if high efficacy treatments have long term safety concerns and/or if the efficacy with time becomes more comparable between treatments. Both conditions are met in the care of MS patients. Increasingly patients are starting with higher efficacy treatments with a substantial number of patients being treated with anti-CD20 treatments. However, anti-CD20 treatments with time are associated with increased risk of infection particularly as IgG levels begin to decrease. In work done in collaboration between the University of Colorado and New York University looking at 1000 patients on rituximab we noted an over 3-fold increase in infections if IgG was <500 mg/dL (Table) (7). Additionally, the difference in efficacy between therapies becomes less pronounced with time. The difference in efficacy between natalizumab and rituximab (together forming the infusible high efficacy group) decreases over time as compared to dimethyl fumarate and fingolimod (oral mid-tier efficacy group; Figure) (8).

Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV Antibiotics^

	All Infections	No Infection	Total
IgG Value: <500 mg/dL	9 (23.7%)	29 (76.3%)	38
IgG Value: Always ≥500 mg/dL	52 (7.4%)	648 (92.6%)	700

^ Chi-square test **p-value: 0.004**

Logistic Regression Analysis			
	N	**Odds Ratio** (95% CI)	p-value
Unadjusted Logistic Regression	738	**3.87** (1.74, 8.60)	**0.002**
Adjusted Logistic Regression*	646	**3.15** (1.16, 8.55)	**0.024**

Note: Lab value<500 mg/dL at least once at any time, not necessarily at time of infection

*Adjusting for age at first infusion, gender, disease duration, diagnosis (Relapsing MS, Progressive MS or Other), and disability at baseline

Table. Infections resulting in Hospitalization, Extended Dosing Antibiotics or IV Antibiotics in patients with IgG <500. There was over a 3-fold increased risk even after adjusting for other factors.

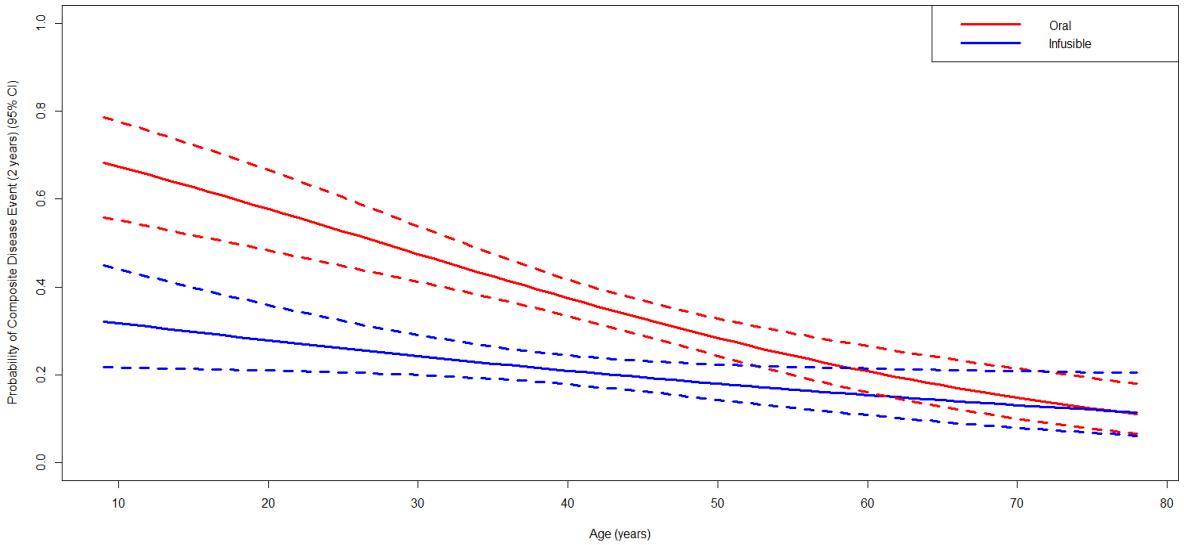

Figure 1. Relative efficacy of disease modifying therapies in the treatment of MS. Rituximab and natalizumab (Infusibles, blue) are more efficacious than the oral treatments composed of dimethyl fumarate and fingolimod (red). As patients with MS age, the likelihood of disease activity decreases and the difference between orals and infusibles becomes negligible. Dashed lines represent the 95% confidence intervals (8).

Because of the decreasing efficacy of higher efficacy treatments and the increased risk with age and time on treatment, a strategy to switch to safer and more convenient therapies becomes a rational treatment option. This approach, known as de-escalation, may help mitigate risk but still maintain good efficacy in patients with MS. One such study to demonstrate the impact of de-escalation therapy was STRATEGY (Multicenter, Retrospective, Observational Study Evaluating Real-world Clinical Outcomes in Relapsing-remitting Multiple Sclerosis Patients Who Transition from Tysabri® [Natalizumab] to Tecfidera® [Dimethyl Fumarate])(4). This retrospective study evaluated the effectiveness of dimethyl fumarate (DMF) in patients de-escalating from natalizumab across 45 US Centers. Eligible patients were ≥18 years of age at study enrollment; had a diagnosis of relapsing remitting MS; had received ≥12 months of natalizumab prior to de-escalating to DMF and followed for 12 months post de-escalation. Of the 506 eligible patients, the mean age was 47 years at initiation of de-escalation with DMF therapy and 12.7 years since MS diagnosis. Mean duration on natalizumab was 3.4 years. The overall probability of a relapse one year after de-escalation from natalizumab to DMF was 19.6% (93/506 with 15% experiencing one relapse, 3% experiencing 2 relapses, and 0.6% experiencing 3 relapses). With regards to safety outcomes, 8% of patients reported ≥1 adverse event following de-escalation leading to DMF discontinuation, the most common being gastrointestinal disorders. About 1 % (7/506) of patients were hospitalized due to more severe relapses in the year after DMF initiation. While this study showed evidence of some of the benefits of de-escalation, there were some limitations associated with it. Primarily, all adult patients, regardless of their age and disease stability status were included in the study. This resulted in some continued disease activity in the form of relapses post de-escalation. This was a retrospective study resulting in the ability to capture limited outcomes as acknowledged by the authors.

Teriflunomide, another oral DMT, was used as a de-escalating agent for patients with relapsing forms of MS who were previously taking natalizumab. Edwards and colleagues examined the safety and efficacy in patients de-escalating from natalizumab to teriflunomide with relapsing forms of MS(5). The authors examined 51 patients with a mean age of 47 years, who had completed 3.4 years on natalizumab and were relapse free in the 12 months of natalizumab prior to de-escalation to teriflunomide. De-escalation to teriflunomide, occurred

at 14mg daily and within 4 weeks after their last dose of natalizumab. Relapse assessment, EDSS and MRI scans were conducted at baseline and monthly for 6 months until month 12. MRI results showed 15 patients with new MRI activity during the first 12 months (29.4%), of which 14 had contrast enhancing lesions. Three patients (5.8%) required a change of DMT due to MRI progression. Three patients (5.8%) dropped out of the study due to adverse events or lack of efficacy.

The limited experience with de-escalation therapy has shown the following: 1) all patients regardless of age have been included in these evaluations; 2) disease stability has been limited to patients who have been merely relapse free in the year prior to de-escalation; and 3) the only high efficacy DMT examined prior to de-escalation has been natalizumab. These results demonstrate that between 70-80% of patients show no disease activity in the first 12 months following de-escalation. The studies above also have focused on natalizumab, a therapy that can demonstrate a prompt resumption of inflammatory activity which is a known side effect of natalizumab interruption. These gaps demonstrate a critical need to further explore the concept of de-escalation on efficacy and safety outcomes in patients who have been stable for longer periods of time and de-escalating from other high efficacy treatments such as anti-CD20 treatments, which has not been associated with rebound disease activity. The investigation of anti-CD20 agents is of particular importance as the efficacy of the medication after discontinuation is related to a relatively slow re-population of CD20 cells. This would allow a greater window for the next therapy to become active as seen in the HERMES study allowing for de-escalation to fully take effect (6).

A transition to ozanimod may provide some advantages over other treatments such as a transition after B-cell depletion. Ozanimod is a once daily oral medication providing great convenience with great tolerability. This provides an advantage over fumarates, which are twice daily treatments that have a high rate of GI intolerability (9). Additionally, ozanimod may have advantages over fingolimod, which was the first S1P partial agonist approved in the treatment of MS patients, in that it may be safer. There are no reported cases of fungal meningitis such as cryptococcus and patients appear to have better responses to vaccination (10). The efficacy of ozanimod was evaluated in two phase III trials that suggested efficacy similar to dimethyl fumarate and fingolimod (11, 12). Additionally, ozanimod is not associated with developing hypogammaglobulinemia which as described above can occur with B-cell depletion and is associated with infections.

Objective

We propose a multi-center pilot study, which aims to evaluate safety and efficacy of ozanimod as de-escalation therapy in clinically stable MS patients previously treated with anti-CD20 therapy. This will be evaluated using the endpoints listed below.

Primary Endpoints:

1) Number of new T2 lesions on MRI scans over at least 36 months of follow up.
2) Serious infections are defined as infections requiring hospitalization, intravenous antibiotic use, or prolonged antibiotic use for treatment of an infection for at least 30 days.

Secondary Endpoints (from baseline to 36 months):

1) Evidence of relapse activity –protocol defined relapses are described below. Additionally, suspected relapses will be evaluated.
2) IgG and IgM levels
3) All infections including opportunistic infections

<u>The following will be described only on the open label arm:</u>

4) 6 months Confirmed Disability progression (CDP6): measured by the EDSS assessed at baseline and every 6 months. CDP6 is defined as an increase in Expanded Disability Status Scale (EDSS) score of ≥1.5 if baseline EDSS

was 0; or ≥1.0 points if baseline EDSS was ≥0.5-≤5.5; or by ≥0.5 points if baseline EDSS ≥6, sustained over two consecutive visits, in the absence of a relapse.

5) No Evidence of Disease Activity (NEDA-3), percent of patients not meeting any of the following criteria:
   a. Evidence of Relapse activity - collected every 3 months via phone calls/clinic visits.
   b. MRI disease activity - presence of new T2 lesions from MRI scans conducted at any timepoint.
   c. 6 months Confirmed Disability progression (CDP6): measured by the EDSS assessed at baseline and every 6 months. CDP6 is defined as an increase in Expanded Disability Status Scale (EDSS) score of ≥1.5 if baseline EDSS was 0; or ≥1.0 points if baseline EDSS was ≥0.5-≤5.5; or by ≥0.5 points if baseline EDSS ≥6, sustained over two consecutive visits.
6) Neurofilament light (NFL) and Glial Fibrillary Acid Protein (GFAP) levels
7) Brain parenchymal and thalamic volume loss
8) Adverse events

Exploratory Measures (from baseline to 36 months):

1) a 4 points or 10% change in cognition (measured by the Symbol Digital Modalities Test)
2) a 20% change in hand function (measured by the 9-hole peg test)
3) a 20% change in walking speed (measured by the 25-foot walk speed)
4) Multiple Sclerosis Functional Composite (MSFC) defined as a change in any of the above three criteria
5) a minimum of 5% in change scores in PRO outcomes to include treatment satisfaction (TSQM), MS fatigue scale (Modified Fatigue Impact Scale [MFIS]), or quality of life (MSIS-29)
6) we will also describe changes in employment and full employment proportions

Study Population

Prospective: Twenty-four patients ≥18 years of age with a minimum of 2 years of MS disease stability (no relapse or new magnetic resonance imaging lesions) and at least two years of experience on an anti-CD20 agent prior to initiating de-escalation with ozanimod (Zeposia®) will be followed for 36 months post de-escalation.

Retrospective secondary Use Cohort: At least 500 patients at Cleveland Clinic or at the University of Colorado on anti-CD20 treatment for at least 2 years since March of 2020 (date of ozanimod approval), who also meet the above inclusion and exclusion criteria, with follow up of an additional 36 months on B-cell depleting treatments.

Inclusion criteria:

• Participants have been diagnosed with relapsing forms of MS and have had multiple sclerosis related symptoms at least 3 years prior to baseline visit
• Male or female participants ≥ 18 years of age at the time of initiation of de-escalation
• Participants do not have evidence of new inflammatory disease activity (no new T2/contrast enhancing lesions, absence of relapses) for a minimum of two years prior to de-escalation
• Participant is taking an anti-CD20 therapy as a DMT continuously for a minimum of two years (e.g., has received at least 3 courses of rituximab, ocrelizumab, ublituximab; 24 months of treatment with ofatumumab; or a combination of treatments whereby the patient has been deemed to be B-cell depleted for 2 years) prior to initiation of de-escalation
• Participants received their last anti-CD20 infusion within 6-12 months or received their last ofatumumab injection within 30 –180 days from Day 1
• Participants must provide written informed consent and be able to comply with the visit schedule and study related assessments
• Participants must be able to undergo a brain MRI without anesthesia
• Woman of Childbearing Potential must agree to practice a highly effective method of contraception throughout the study until completion and willing to follow pregnancy precautions as outlined in Appendix A.

Exclusion criteria:

•Any progression of neurological disability in the year prior to the screening visit that would be consistent with progressive MS

• Participant has an EDSS >6.5

• Participant has a history of other chronic neurological illnesses that might mimic MS with chronic or intermittent symptoms (i.e. ALS, myasthenia gravis, chronic neuropathy, etc.)

• Participant is considering pregnancy in the short term, is pregnant, lactating or has a positive serum beta human chorionic gonadotropin (B-hCG) measured during screening.

• Participant has any other significant medical or psychiatric illness, if uncontrolled, that could jeopardize a subject's health or put them at significant safety risk during the course of the study in the opinion of treating investigator. Examples: uncontrolled hypertension, uncontrolled diabetes, uncontrolled asthma, uncontrolled depression

• Participant has a history of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or cervical dysplasia/cancer that has been excised and resolved)

• Participant has a history in the last 6 months of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure

• Participant has Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker

• Participant has severe untreated sleep apnea

• Participant has a history of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c (HbA1c) > 9%, or is a diabetic subject with significant comorbid conditions such as retinopathy or nephropathy, or a history of uveitis

• Participant has a history or known presence of recurrent or chronic infection (e.g., hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV); recurrent urinary tract infections are allowed.

• Any known or suspected active infection (excluding onychomycosis) at screening, including but not limited to a confirmed or suspected progressive multifocal leukoencephalopathy (PML). Known currently active tuberculosis (TB). History of incompletely treated Mycobacterium tuberculosis (TB) infection, as indicated by: Subject's medical records documenting incomplete treatment for Mycobacterium TB; Subject's self-reported history of incomplete treatment for Mycobacterium TB; Subjects with a history of TB who have undergone treatment accepted by the local health authorities (within 1 year from screening) may be eligible for study entry.

Exclusions related to Medications:

• Concomitant use of a monoamine oxidase inhibitor

• Use of systemic corticosteroids in the last 2 years. (Note: Use of inhaled or topical steroids; use of oral steroids for no greater than 14 days given for a non-MS condition are allowed)

• Prior use of alemtuzumab, mitoxantrone, cyclophosphamide, methotrexate, cyclosporine, or any experimental MS treatment within the last 5 years

• Prior allergy to ozanimod

Exclusions related to Laboratory results:

• Participant has IgG levels <400 mg/dL

• Participant has neutrophils < 1500/µL (1.5 GI/L)

• Participant has an absolute white blood cell (WBC) count < 3500/µL (3.5 GI/L)

• Participant has an absolute lymphocyte count (ALC) < 800 cells/µL (0.80 GI/L).

• Participant has liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) results > 3 x the upper limit of normal (ULN)

VZV testing and vaccination will not be required as part of this protocol. This will be conducted by principal investigator (PI) discretion and could be done as standard of care.

Study Design
Multicenter, Open Label, Prospective Study examining the safety and efficacy of de-escalation therapy to ozanimod (Zeposia®) over 36 months from anti-CD20 therapy for stable patients with relapsing forms of MS. A comparison to patients continuing anti-CD20 treatment will be done with propensity scoring to a cohort of at least 500 patients followed at Cleveland Clinic and the University of Colorado who also meet the above inclusion and exclusion criteria at the time when they could be followed for 36 months. This study will be listed in clinicaltrials.gov once approved.

Data Capture
An electronic data capture system will be generated to provide a standardized tool with clear instructions on how to obtain and submit data. Data will be shared in a secure de-identified manner and stored in a HIPAA compliant manner.

Sites:
- Mellen Center for Multiple Sclerosis Treatment and Research at Cleveland Clinic (PI Devon Conway, MD, MSc)
- Cleveland Clinic Lou Ruvo Center for Brain Health (PI Carrie M. Hersh, DO, MSc)
- The Rocky Mountain MS Center at the University of Colorado (PI Enrique Alvarez, MD/PhD, Coordinating site)

Institutional Review Board Approval
The Rocky Mountain MS Center at the University of Colorado will be the data coordinating/statistical analysis site and the other sites will have their own IRB approval and oversight. Each site will pursue its own IRB approval. A Spanish language consent and advertising will be developed and approved by the IRB. It is expected that recruitment will be primarily with patients who have a treatment relationship at the approved sites, but local advertising will be pursued if recruitment becomes delayed.

Monitoring Plan
The project management team at the Rocky Mountain MS Center at the University of Colorado will monitor compliance and the data for this study at all sites. This team will be independent of the team completing the study. They will ensure that training and delegation logs are completed as a site becomes active. After the first patient is enrolled in the study and at least twice per year, they will review data at all of the sites, remotely, to ensure completeness and accuracy of the entered data. They will also visit each site in person up to 2 times throughout the duration of the study.

Dosing Regimen
Ozanimod will be started 6-12 months after the last anti-CD20 infusion or 30-180 days from their last ofatumumab injection. Ozanimod will be provided by the study.

Ozanimod titration will begin with 0.23mg orally once a day on days 1-4 and followed by 0.46mg (taken as 2 pills of 0.23mg orally once a day) on days 5-7. Subjects will be provided with 2 bottles with 7 pills of the 0.23mg dose to initiate treatment.

Ozanimod maintenance will start on day 8 with 0.92mg daily provided to subjects in bottles of 30 pills of 0.92mg each with enough bottles to last until the next appt allowing for enough excess to cover the window around each visit.

Subjects should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the subject vomits the capsule, he/she should be instructed not to take another capsule on the same day, but to take the next dose at the regular time on the following day. If a dose is missed during the first 2 weeks of treatment, or for more than 7 consecutive days during Days 15-28 or for more than 14 consecutive doses, reinitiate treatment using the 7-day titration regimen.

Biorepository

Leftover samples from this study will be stored in the Rocky Mountain MS Center Biorepository (University of Colorado COMIRB 12-0968), if the subject consents to this. All samples collected in this study at external sites to the University of Colorado will be de-identified at the time of transfer to protect the confidentiality of the participants.

Statistical analysis:

The emergence of new T2 lesions and serious infections (primary outcomes) will be described using product-limit estimates (Kaplan-Meier plots). Proportions of patients with disease activity will be reported, along with 95% confidence intervals. With 24 patients, if there is *no evidence of disease activity* in any patients in 36 months, we are 97.5% confident that the true rate is below 14.2%. Similarly with 1, 2, and 3 patients *with* observable disease activity in 24 months, we are 95% confident the true rates are between 0.1-21.1%, 1.0-27.0% and 2.7-32.4% respectively. Product-limit estimates (Kaplan-Meier plots) will also be used to analyze relapses and IgG and IgM levels.

A comparison will be made between new T2 lesions and serious infections in the open label de-escalation arm to the CD20 maintained retrospective cohort over 36 months using propensity score (PS)-adjusted analysis. Baseline covariates healthcare providers find important in DMT decision-making will be incorporated into the PS model: demographics (e.g. age, sex, race, ethnicity), baseline clinical characteristics (e.g. disease course, disease duration, prior DMTs, relapse status, PDDS), baseline radiographic characteristics (e.g. prior T2/GdE lesions), and PROs (Neuro-QoL). The investigators will plan to use baseline information in selecting cases to meet the positivity assumption (e.g., age ≥40 years old and started B-cell depletion recently enough for study entry). The appropriateness of using a PS-adjusted analysis will be determined by creating a PS density plot to ensure there is sufficient overlap between the two cohorts. The PS technique used [e.g., 1:1 greedy matching, Inverse probability of treatment weighting (IPTW)] will be determined based on the best overall covariate balance using the following definition: excellent covariate balance defined as an absolute standardized difference <10% on the means of the covariate across the two treatment strategies. A more robust PS-adjusted analysis will be conducted using the linear PS, for which excellent balance will be determined as a linear PS < 50%. Standardized difference plots will be used to determine the PS technique yielding the best overall covariate balance. Once this is determined, these adjusted data will be used in making conclusions on the above comparative endpoints. Rosenbaum bounds will be used to measure the amount of hidden bias in the model that will help determine the robustness of statistically significant results. Because of the low number of expected events, exact methods for proportion tests may be required, such as Clopper-Pearson exact confidence intervals and Fisher's exact association test. Interim analysis will be done at 12 and 24 months.

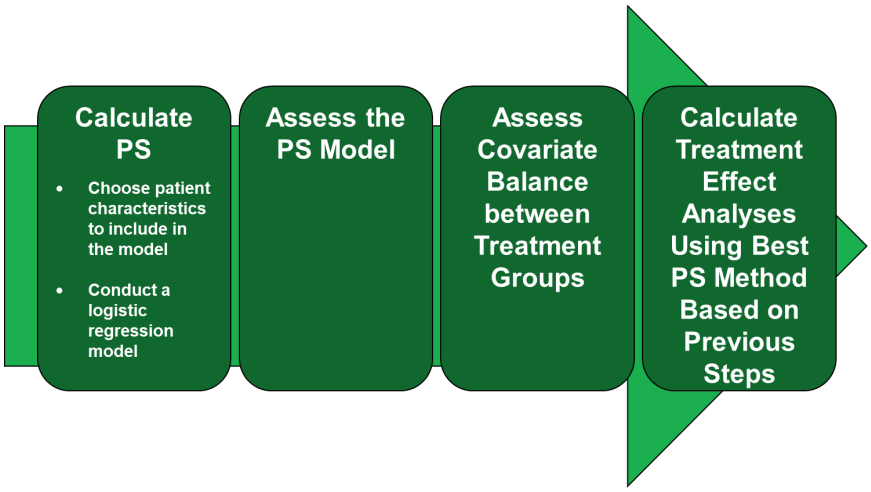

Figure 2. Propensity Score (PS) methodology.

MRI protocol:
A short MRI protocol will be employed to evaluate for new T2 lesions, which is one of the primary end points for this study. High resolution T2 FLAIR sequences will allow for evaluation of new lesions and characterize their localization, size, and shape to evaluate if they are consistent with MS. To aid in this decision making, central vein sign will be evaluated with T2* sequences. To measure acuity of lesions, diffusion imaging will be obtained. A high resolution T1 sequence will allow for determination of volumetrics. The following MRI sequences will be obtained:

1. MPRAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) - Whole brain T1-weighted images acquired using 3D fast spoiled-gradient recalled acquisitions (T1-3D-FSPGR) with in plane resolution of 1x1 mm with 1 mm slice thickness (isotropic voxel dimensions).
2. Central vein sequence - Whole brain 3D EPI T2*-weighted gradient recalled images with 0.7 mm isotropic voxels.
3. 3D T2 FLAIR (Fluid Attenuated Inversion Recovery) and 3D T2 images - Whole brain 3D T2-weighted images with bright and dark fluid contrast acquired via fast spin echo 3D T2 SPACE technique with 1 mm slice thickness and isotropic voxel dimensions.
4. Diffusion weighed images (DWI) with apparent diffusion coefficient (ADC) maps – 2D whole brain DWI images with 0.6 mm x 0.6 mm x 3.0 mm voxels and b=1000 weighing.

Risks/Safety:
New T2 MRI lesions:
MRI images will be read by a centralized neuroradiologist who is blinded to patient identifiers. A new lesion will be defined as any new T2 weighed lesion at least 3 mm in size felt to be due to MS. For subcortical lesions, this will include a sensitivity analysis including only those lesions with a central vein.

Relapse:
If a participant has either new symptoms to suggest a relapse and/or a new/enlarging brain MRI lesion they will be evaluated for a relapse and be considered for remaining on ozanimod or through standard of care switched to restarting a B-Cell depleting DMT or an alternative DMT. Relapse treatment will be at the discretion of the treating provider. All subjects including those who discontinue drug, for any reason, will continue to be followed at all study time points and will have all study procedures if they decide to continue in the study to help evaluate efficacy and safety.

A relapse will be defined as the appearance of new neurological symptoms or worsening of pre-existing neurological symptoms and accompanied by objective change in the neurological examination corresponding to that symptom by the examining clinician which could include the treating clinician. Once the subject feels that they have experienced a relapse, the subject will contact the PI and/or study coordinator as soon as possible. Events may also be identified during study visits or follow-up telephone calls. It is important that the subject be seen as soon as a potential relapse is identified. Subjects should be seen as soon as possible and ideally 7 days of onset of symptoms.

Each Relapse event will be categorized on CRFs as one of the below:

- Protocol defined relapse: defined as an increase of ≥ 0.5 EDSS, or 2 points increase on 1 of the functional system scores (FSS), or 1-point increase on ≥ 2 of the FSS. The increase in FSS scores must be related to the neurological symptoms which were reported as new or worsening and the change must affect the selected FSS (i.e., pyramidal, cerebellar, brainstem, sensory, or visual, excluding cerebral, bladder or bowel).
- Suspected relapse: Relapse that fails to meet the above changes in EDSS but is considered by the examining clinician to be a relapse. Symptoms must have lasted at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days.
- Pseudo-relapse, i.e. a worsening of pre-existing neurological symptoms in the context of any significant stressor, including, but not limited to, infection, physical, psychological, or mental stress, as determined by the treating physician; or other symptoms felt not to be related to MS.

Adverse events**:** An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or condition occurring after starting the study even if the event is not considered to be related to study conditions or assignment. Study conditions or assignment includes assignment to continue or discontinue prior DMT. Medical conditions and diseases present before starting the study are only considered AEs if they worsen after starting the study and if they are self-reported by the patient. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by nondirective questioning of the patient at each visit during the study, including monthly phone calls. Only those AEs self-reported by the patient are documented. All AEs must be recorded with the following information:

1. the severity grade (mild, moderate, or severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final examination)
4. whether it constitutes a serious AE (SAE)

Serious adverse events such as hospital admissions for > 24 hours, new significant medical diagnoses such as cancer (other than basal cell carcinoma), and MS relapse requiring corticosteroid use will be ascertained at each visit. SAEs should be reported to the sponsor via email.

Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be formed to help monitor the study for feasibility to continue the study and adverse events (AEs). This board will consist of two board-certified neurologists not otherwise associated with the study and a biostatistician. They will meet yearly after the first patient is enrolled until the last patient completes the study.

It is possible that, despite a prolonged period with no new inflammatory disease activity, those who de-escalate their DMTs will have an increase in inflammatory disease activity. The DSMB will be required to consider discontinuing the study if either of the following occurred at either interim analysis time point:
- Efficacy: one half of the subjects enrolled in the study experience a new MRI lesion concerning for MS. These patients would be expected to have a low rate of accumulation of new T2 lesions but patients with MS can develop new lesions. As a reference, according to DAYBREAK CSR (Table 14.2.2.3): over 3 years in the extension study of the phase 3 study RADIANCE, 56% of the subjects continuously treated with ozanimod developed new/enlarging T2 lesions relative to the baseline of the open-label extension study. (13).
- Safety: Evaluate serious AEs that to the discretion of the DSMB should lead to the discontinuation of the study due to the placement of subjects at significant risk to continue in the study.

Additionally, any of the sites or the sponsor can decide to stop the study at any time due to concerns for safety. There will be a regular meeting with the site PIs and BMS that will occur at least quarterly and more frequently as needed to review recruitment and safety events.

Study Timeline
Recruitment will be over 9 months (approximately 1 patient per site per month). Patients, including dropouts, will be followed for 36 months. Interim analyses will be done every 6 months with reports/updates made at ACTRIMS/AAN and ECTRIMS.

Visit schedule:

Visit	Screening (<30 days before baseline)	Baseline (can be with screening)	Month 3 (+/- 30 days)	Month 6 (+/- 30 days)	Month 12 (+/- 30 days)	Month 18 (+/- 30 days)	Month 24 (+/- 30 days)	Month 30 (+/- 30 days)	Month 36 (+/- 30 days)
Consent	X								
CBC with diff, CMP	X		X	X	X	X	X	X	X
IgG and IgM	X				X		X		X
Biomarker evaluation^	X		X	X	X	X	X	X	X
B-cell levels*	X			X	X	X	X	X	X
Inclusion/ exclusion review	X								
Demographic	X								
Pregnancy evaluation%	X		X	X	X	X	X	X	X
EKG	X								
OCT$	X		X						
EDSS	X			X	X	X	X	X	X
MRI	X			X		X			X
MSFC@	X			X	X	X	X	X	X
PROs#	X			X	X	X	X	X	X
Drug Dispensing		X		X	X	X	X	X	
	Relapse, pregnancy, and AE/tolerability assessments will be done in above visits and the following phone calls (+/- 5 business days): Month 1, 9, 15, 21, 27, 33								

^ NFL, GFAP, biobank samples [Patients will have the option to consent to storing blood (serum and peripheral blood mononuclear cells (PBMCs) in the University of Colorado Biorepository].

* PBMCs sent to the University of Colorado for evaluation of B-cell levels.

% Pregnancy can be assessed via history and does not require a serum/pregnancy test. This can be done via standard of care if there is concern for current pregnancy. If a pregnancy is identified, the patient will be followed for 90 days after treatment discontinuation to collect the following information: the outcome of your pregnancy including spontaneous or voluntary termination; details of the birth (full-term, premature, or involves complications); the presence or absence of any birth defects, abnormalities, or complications; and the health status of your child.

$ OCT – Not required on all subjects but will be performed on subjects at high risk for macular edema (e.g., Type 2 Diabetes) and to be performed as standard of care and will be done via standard of care. A history of uveitis is exclusionary.

@ MSFC to include SDMT (oral and written), 9-hole peg test, and 25-foot timed walk

PRO outcomes to include treatment satisfaction, employability status, fatigue, PDDS, MFIS, and quality of life (MSIS-29).

Unscheduled visits for further discussion of relapses, pregnancy, AEs, and/or drug tolerability will be done as determined by the site PI or sub-investigator. If there is a concern for a relapse, a history and physical exam by the PI or sub-PI to help assess if there was a relapse, a pseudorelapse, or something else. These visits will include as much as possible NFL, GFAP, B-cell levels, biobank samples, EDSS, MSFC, and PROs. For pregnancy assessments, a discussion will include stopping treatment if the subject is pregnant and collection of outcomes as described in appendix A should be conducted.

Funding/Budget

The planned budget is $2 million and sponsored by BMS. The University of Colorado will serve as the primary site and will subcontract with the remaining sites. See separate documentation for full budgetary details.

References

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Appendix A - Risks Associated with Pregnancy

The risks to an unborn child or nursing child from ozanimod are not known at this time. Ozanimod should not be taken by pregnant or nursing women.

Studies in animals have shown that ozanimod can harm a fetus, and it is possible the study treatment may harm a nursing child or may cause a miscarriage.

If you are a woman

If you are pregnant, planning to become pregnant, or you are nursing a baby, you should not take part in this study. The study doctor will discuss effective birth control methods with you if you are able to become pregnant. This is to make sure that you do not become pregnant while in the study. Your chosen form of birth control must be effective by the time you receive your first dose of study drug. For example, birth control pills should be started at least 28 days before your first dose of study drug.

If you can become pregnant,

- pregnancy will be assessed at your study visits, and you must avoid any sexual activity that may lead to pregnancy or
- you must use one of the approved options for birth control while taking the study drug and for at least 90 days after your last dose of study drug.

Approved options are any one of the following highly effective birth control methods:

- Hormonal contraception (for example, birth control pills, intravaginal ring, transdermal patch, injection, implant);
- intrauterine device (IUD);
- tubal ligation (tying your tubes);
- a partner with a vasectomy; or
- abstinence.

Certain other drugs may reduce the effectiveness of hormonal birth control treatments during and up to 30 days after discontinuation of these concurrent therapies. Please talk to your doctor for further information about birth control treatments.

You must inform the study doctor, if at any time during the study:

- your birth control method changes, or
- you experience a problem with your current birth control method.

If your ability to become pregnant changes (for example, you have an IUD removed, accidently miss taking any of your birth control pills, or enter menopause), you must inform and discuss with the study doctor or nurse about other birth control methods.

If you suspect that you have become pregnant during the study or within 90 of the last dose of study drug, you must tell the study doctor right away. Your study doctor must then require you to stop taking the study drug. Your study doctor will want to check on you during the pregnancy and ask you questions about the pregnancy.