Protocol Title: **People with Multiple Sclerosis treated with Ocrelizumab and GLP-1 agonists**

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	n/a
IND / IDE / HDE #	n/a
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Adults with Impaired Decision-making Capacity ☐ Neonates of Uncertain Viability ☐ Pregnant Persons ☐ Prisoners (or other detained/paroled individuals) ☐ Students or Employees
Sample Size	100
Funding Source	Genentech
Indicate the type of consent and HIPAA to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver or alteration of HIPAA Authorization ☐ Waiver or Alteration of Consent Process ☐ Limited Data Set with a Data Use Agreement
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

STUDY OVERVIEW AND RATIONALE:

Background and Objectives

Multiple sclerosis (MS) is a chronic demyelinating disease with treatment options that have been evolving significantly with the rise of Disease-Modifying Therapies (DMTs). These medications

are commonly used to slow progression and treatment outcomes vary depending on comorbidities and lifestyle factors.

At least 15% of people are clinically obese at the time of MS diagnosis.[1] Obesity is also a risk factor for the conversion of radiologically isolated syndrome (RIS) (early MS) to first attack and negatively influences MS functional outcomes and disability.[2-4] Ocrelizumab is increasingly the disease modifying treatment of choice for people with MS in the USA and globally. Many Ocrelizumab-treated patients are starting to administer (with or without physicians' guidance) the glucagon-like peptide-1 (GLP-1) agonists[5], such as semaglutides, for diabetes, weight loss, and an increasing number of FDA-approved and experimental indications. Many other patients with MS would like to start this drug class to induce weight loss. Others may be influenced by early phase data that suggest the GLP-1 medication class is neuroprotective, reduces cardiovascular disease risk, and/or allows weight maintenance to return to regular aerobic physical activity. [6-8]

Study Significance and Motivation
Although there is growing interest in understanding how metabolic interventions may intersect with immunotherapies in MS nearly no data exist on the co-treatment of people with MS with Ocrelizumab and a GLP-1 agonist (e.g. Wegovy). In 2023-24, we performed a small, retrospective study of ~50 people with MS and their weight loss and tolerability of GLP-1 agonists in Boston, many of whom were treated with Ocrelizumab (Udawatta et al. *Neurol Sci.*2024 doi: 10.1007/s10072-024-07701-7).[9] Others have followed with observational data on GLP-1 in cohort studies or have work in progress.[10,11]

However, the sample sizes in existing published work are so far too small to conclude the outcomes of MS patients treated specifically with Ocrelizumab. Also, patient-based assessments and reports were lacking as early work has been largely retrospective and spanning the time when the GLP-1 agonists were only approved for MS patients with comorbid diabetes mellitus.

RESEARCH DESIGN AND METHODS:

Study Aims
In this prospective study, there are two main aims:

(1) To implement patient-reported outcome measures (PROMs) in **60** people with MS *already treated* with both Ocrelizumab and a GLP-1 agonist to assess progression and ambulation, while recording drug tolerability and potential adverse events, weight loss, disease-based outcomes focused on progression, and MS-focused quality of life; and
(2) Enroll a single-arm, open-label trial of **40** Ocrelizumab-treated MS patients who are soon *starting GLP-1 agonists*, monitored prospectively for 2 years to measure MS **progression** (clinical disability worsening, stability or improvement) every 3 months, including (a) clinical assessments (e.g. EDSS, 25-foot timed walk, SDMT) as used in the ORATORIO trial of Ocrelizumab, (b) PROMs on progression in MS including fatigue, ambulation distance, mood; and (3) simple objective biomarkers of disease (e.g. plasma neurofilament light chain, glial fibrillary acidic protein).

Overview: Aims 1 and 2 will recruit participants simultaneously but draw upon MS participants at different points in their GLP-1 agonist treatment. Participants can enroll in either the cohort of Aim 1 (in-person or remote) or the open label trial of Aim 2 (in-person only), not both aims. All participants will be Ocrelizumab-treated for MS upon study enrollment.

Study Endpoints
The primary outcome measure is **PIRA** (progression independent of relapse activity), based primarily on clinical assessment, dichotomized as present or not.[12]

For Aim 1, the cohort, patient-derived disability status (PDDS) score, and ambulation score (self-reported) will be the primary endpoints of interest.

For Aim 2, the clinical trial, PIRA will be measured pre-GLP-1 start and at study end (week 72). A composite score of disability, similar to the ORATORIO[13] trial will be constructed including EDSS score, 25-foot timed walk, 9-hole peg test, and SDMT score.

Study Interventions/ Investigational Agent
Glucagon-like peptide-1 agonist agent is the study agent of interest. This study will not supply the GLP-1 drug but depend on the patient's clinical prescription of this drug. Similarly, all participants will be treated with Ocrelizumab for the indication of MS; however, the study will not provide Ocrelizumab as it will be part of the participant's routine clinical care.

Study Procedures
Inclusion Criteria, Aims 1 and 2:

1) Diagnosis of MS (2019 revised McDonald criteria) of any type (PPMS, RRMS, SPMS) by a neurologist,
2) Adult age 18-70 years,
3) BMI >=24.0 kg/m^2,
4) Taken at least one dose of Ocrelizumab prior to study entry,
5) EDSS <7.0,
6) Able to provide individual informed consent,
7) MRI available to confirm the diagnosis of MS.

Exclusion Criteria, Aims 1 and 2:

1) Prior exposure to Mavenclad, Lemtrada, Cyclophosphamide, stem cell transplant or related bone marrow suppressive treatment,
2) Current clinical trial participant,
3) Unable to speak a language for which translation can be found in the hospital system,
4) Unclear documentation of MS diagnosis or prior or current MS treatment,
5) Relapse within the past 3 months,
6) Recent major surgical procedure in the past 6 months,
7) Exposure to steroids (systemic) within the past 3 months,
8) Not on Ocrelizumab in the past >9 months,
9) Moribund status,
10) Underweight or experiencing protein malnutrition,
11) Unable to provide consent voluntarily due to reasons of capacity or other reasons (e.g. incarcerated, dementia, etc.),
12) Unable to complete the study activities for any reason as deemed by the study investigator.

*Additional Inclusion Criteria Aim 1:

8) Exposed to GLP-1 agonist treatment in the last 3 years or less, or starting on a GLP-1 agonist in the coming <3 months,
9) Willing to report monthly patient-reported outcomes remotely or in-person.

*Additional Inclusion Criteria Aim 2:

8) Able to present for baseline and follow up in person,
9) Unexposed to a GLP-1 agonist in the past year,
10) Starting on a GLP-1 agonist in the next <6 months,
11) Plan to be exposed to GLP-1 agonist for a minimum of 72 weeks following enrollment.

Participant Population(s)

Accrual Number:	Category/Group:	Consented/Enrolled:
Local	Individuals with MS already treated with Ocrelizumab and GLP-1 agonist	60
	Ocrelizumab-treated MS patients initiating GLP-1 agonist	40
Study-wide		
Total:		100

RECRUITMENT METHODS:

Potential participants will be identified through online research advertising webpages (e.g., ClinicalTrials.gov, Northwestern's clinical trials website), the investigator's connections with MS neurologists in the practice and surrounding practices, advertisements in MS clinics, the National MS Society local chapter's and national websites, MS physician networks, social media directly to patients, flyers in the medical infusion center, weight loss and nutrition clinics in the region, and through clinic newsletters and the word of mouth.

Interested patients will be screened through an online RedCap™ form for the study's eligibility criteria. Medical records review will occur by the investigators to ensure the criteria are met. Participants will then be called by telephone or met in person to describe the study procedures in detail.

CONSENT PROCEDURES:

Consent will be taken by a trained study team research coordinator or physician. All consent will be written on a standardized consent form, in English. Consent may be performed electronically using REDCap e-sign with an institutionally approved account. Participants will be given >24 hours to review the consent form and provide consent. Given the complexity of the study tasks including multiple self-reported variables, only participants who are able to provide their own consent will be enrolled.

Vulnerable Populations

Vulnerable populations will not be enrolled. Participants who lack capacity to voluntarily consent (e.g. institutionalized, dementia) are excluded as per the criteria listed above.

STUDY PROCEDURES:

Aim 1 will allow fully remote participation, drawing from geographically diverse settings throughout the USA. Participants in Aim 1 do not need to visit the study site in person or be

independently mobile but must be continuously available during the study timeframe remotely for PROMS and study surveys and calls.

Participants will be enrolled for an estimated 72 weeks: Measurements will be requested every four weeks (i.e. q28 days) on a specifically designed survey instrument for MS participants. Participants will be asked to report medication dosing, adherence to medicine, tolerability, weight, height, and exercise activities. Self-reported scales will be administered to the participants as well (measuring disability, fatigue, mood, and quality of life).

Participants must be currently on Ocrelizumab (last dose within the past <6 months) and currently taking a GLP-1 medication.

Participants will be contacted and interviewed via Zoom every 6 months to ensure study procedures are going as planned, verify data reported on medication and MS disease history, and ensure study procedures are operating smoothly. Participants who do not complete the surveys within 7 days of the scheduled timing will be contacted by a study coordinator by phone up to 3 times. Participants will also be asked to report any medication changes, dose changes, or discontinuations if they occur at any point between study visits.

Participants will be enrolled until a total of 40 individual participants are reached. Study procedures for each group are listed in Tables 1 and 2. All scheduled events will be part of the study and not part of routine clinical care.

Table 1: Measurements of MS Participants in Aim 1 (Cohort): Frequency and Scale

Measure	***Frequency of Reporting***	***Scale***
Weight	Monthly	kg or lbs
Height	Baseline	cm or inches
Waist, Hip, Limb Circumferences	Monthly	cm or inches
Ambulation score	Monthly	Kurtzke Scale
Disability Score	Monthly	PDDS
Step Count	Monthly	Average daily number on phone or step counter if available
Fatigue	Monthly	Fatigue Severity Scale
Mood	Monthly	Beck Depression Inventory
Quality of Life	q3 months	MS-QOL-54 survey
Intolerabilities	Monthly	Self-reported, qualitative, categorized – gastrointestinal, injection site, infections, etc.
Adherence	Monthly	Number of doses taken/ Total Prescribed doses of GLP-1
Axonal degeneration	Baseline and end of study (if possible)	Neurofilament light chain (serum)
New attacks or lesions	Ad hoc	Reported event if occurs

Table 2: Measurements of MS Participants in Aim 2 (Single-Arm Open-Label Trial)

	Screening	**Baseline**	**Week 24**	**Week 48**	**Week 72**	**Unscheduled Visit (e.g. Relapse, Early Withdrawal)**
Clinical & MS Relapse History	X	X	X	X	X	X

Medication Review	X	X	X	X	X	X
Physical Examination	X		X	X	X	X
Waist, Hip, Limb Circumferences		X	X	X	X	X
Skin Fold Thickness		X	X	X	X	X
Neurological Examination	X	X	X	X	X	X
EDSS & Ambulation Score		X	X	X	X	X
Vital Signs (ht, wt, BMI, blood pressure, heart rate, respiratory rate)	X	X	X	X	X	X
PDDS		X	X	X	X	X
PROMS		X	X	X	X	X
QOL54-MS		X	X	X	X	X
Medication Adherence Questionnaire (GLP-1-focused)		X	X	X	X	X
25-foot timed walk test		X	X	X	X	X
Food Frequency Questionnaire		X	X	X	X	X
Physical Activity Questionnaire		X	X	X	X	X
9-Hole Peg Test		X	X	X	X	X
SDMT+PASAT		X	X	X	X	X
Blood Draw: CBC/differential +Chemistry	X					X
NFL-2, plasma		X	X	X	X	X
GFAP, blood		X	X	X	X	X
Vitamin D		X				X
Beta-HCG (urine) (invoiceable)	(X)	(X)	(X)	(X)	(X)	(X)
MRI Brain, 1.5T (not billed to study)	X	X			X	X

Allocation and Blinding

All participants will be treated with the two drugs of interest: Ocrelizumab and the GLP-1 agonist. The participants will be blinded to the study outcome of interest, i.e. progression or PIRA. The investigators will not be blinded to the study outcome. The participants will not have access to their prior PDDS scores on file, earlier in the study. The EDSS raters will not have access to the prior EDSS scores on file, earlier in the study. The statisticians will not be blinded to the study outcome.

Criteria for Study Drug Discontinuation in a Single Participant
Reasons for GLP-1 agonist drug discontinuation will be at the discretion of the treating prescriber include: (1) laboratory test abnormalities (e.g. transaminitis) whether related to the drugs or not; (2) intercurrent illness; (3) severe intolerance to the GLP-1 agonist; (4) lack of access to the GLP-1 drug within an affordable range; (5) patient preference; (6) achieved weight target earlier than anticipated; or (7) any other reason as determined by the prescribing physician or study principal investigator.

Criteria for Study Withdrawal of a Participant
Participants who discontinue GLP-1 agonist drugs for any reason, including tolerability, cost, desired weight loss outcome, etc., will continue to be observed until the end of the study period. It is possible that participants will have periods of discontinuation and then resume GLP-1 agonist treatment. The participant will be observed until (a) week 72 visit (i.e. end of study period), (b) participant withdrawal with no consent to continue monitoring, or (c) investigator-decided withdrawal of a participant from the study (e.g. severe medical illness preventing study completion, departure far from study site, etc.).

Participant Compensation for Involvement in Research Procedures
Aim 1: Each participant will receive 75 USD every 3 months with a total of up to **600 USD**.

Aim 2: Each participant will receive 150 USD at baseline and 100 USD every subsequent visit occasions and then 150 USD at the final study visit with a total of up to **500 USD**.

Participants will have the option to receive cash or a gift card. Participants who receive cash will need to provide their social security number for the reporting of taxable income to the Internal Revenue Service, according to applicable laws.

There is no anticipated drug development or future product anticipated in this study. A study participant will not have any right to compensation or ownership interest related to such development.

RISKS AND BENEFITS:

Risks to Participants
Participants in this study may have side effects of the medications under investigation including both Ocrelizumab and the GLP-1 medication, although these will be given in the context of clinical care for U.S. Food and Drug Administration (FDA)-approved indications. In particular, the GLP-1 class of medications is known to cause gastrointestinal symptoms, including nausea, vomiting, early satiety, and abdominal discomfort. These are considered reversible, common (approximately 1/3 of all people treated with a GLP-1 medication), and expected. These risks are often mild to moderate and in some cases may lead to early discontinuation of the medication if poorly tolerated. Participants may experience injection-site reactions which could be bothersome.

An additional risk is that participants will be psychologically burdened by repeated testing and surveying throughout the study; however, no clinical harm is anticipated from surveys or the clinical assessments done during the study procedures.

Participants may be subject to an unforeseen data breach during the conduct of the study through data hacking or other means due to human error or technological problems. This may lead to inadvertent disclosure of the MS diagnosis to others. All available measures will be taken to avoid such incidents and warn participants of these risks during the consent process.

Potential Benefits to Participants:
Participants may not directly benefit from this research. Future people living with MS, particularly those taking GLP-1 agonists, are anticipated to benefit from the information gathered in this study. The safety of GLP-1 agonists in Ocrelizumab-treated patients will be established through PROMs, clinical data, and biomarker data. The impact of this emerging drug class on patients with MS will be quantified in terms of weight loss by subgroup (e.g. EDSS level, gender, disease duration, ocrelizumab treatment duration, etc.) given the high sample size. There are new indications for the GLP-1 drug class being proposed (e.g. alcohol cessation, sleep disorders, etc.) and the class may be neuroprotective. If GLP-1 agonists protect against PIRA in people with MS in this study, a new therapy for people with MS may be further studied and developed. Additional data for patients taking Ocrelizumab and GLP-1 agonists concomitantly may also allow patients and providers more data to ensure that MS disease modifying therapy with B-cell depletors are not unnecessarily discontinued.

DATA AND SAFETY MONITORING:

Biobanking of Blood
There will be blood draws in Aim 2's clinical trial population. Aim 1's observational, interactive cohort will have an optional blood draw component. In both cases, the blood tests will involve send out testing for neurofilament light chain and in Aim 2, glial fibrillary acidic protein. The remaining blood will be requested for biobanking for future testing of emerging biomarkers in MS and metablome-related assessments that are not part of the main aims of this study. Participants will be asked if the study team can retain their blood in storage at Northwestern University for future testing. Data and samples may be shared with researchers around the world with the goal of making more research possible. The data and samples will be kept for 5 years after study completion.

Sharing Results with Participants:

Participants will have access to their personal study results at the end of the study after the data are locked and the data are presented, including their clinical scores and their biofluid test results. Future test results, if additional tests are performed on stored blood samples, will be reported back to individual participants only if the test results provide a possibility of clinical relevance to the participant.

There will be no interim results reporting to participants. This is to avoid potential biases in the study as many variables are self-reported.

Data Management and Confidentiality:
The data will be kept in a secure file and analyzed using software that included password protections, encryption, and related security features. Computers will be stored in locked offices. All participants will be given unique study identifiers that they will have throughout the study period. A master file of the participants' personal information and unique identifiers will be kept separately from the study's data collection processes online. Data will be transmitted only using institutional software and secure means such as RedCap that has appropriate institutional security features.

Data will be collected online using RedCap using surveys with forced responses before survey completion to minimize missingness of data. Data will be exported to Microsoft Excel and analyzed using statistical software (e.g. R programming language). Surveys will be scored by the study team using the validated, published metrics (e.g. EDSS, FSS, MS-QOL-54). Variables

of interest will be graphed for distribution (i.e. normalcy) and skew. There will be no data imputation. Missing data will be considered missing completely at random. Interim data analyses will occur every 6 months for reporting to the sponsor. A *p*-value of <0.05 is considered statistically significant.

Aim 1:

Variables of interest will be reported using descriptive frequency-based statistics (e.g. mean, median, range). Subgroups of interest (e.g. by gender, disability level below or above the median, etc.) will be compared using t-tests and tests of two proportions as appropriate. Repeated measures (e.g. weight) will be graphed and displayed. Change in values will be reported (final minus starting weight). If needed to report an outcome, repeated measures analyses, will be made using generalized linear models. Incidence of tolerability issues will be reported as the number of events per number of person-months of observation available.

Aim 2:

This will be an intention to treat analysis. All participants who enroll in the single-arm study will be analyzed to the end of their study participation, either the end of the planned study period or time of withdrawal. Data will be analyzed in aggregate with descriptive subgroup analyses performed with the following variables and subgroupings of interest: (1) sex at birth, (2) age at enrollment below or above the median age, (3) duration of GLP-1 (72 weeks versus early discontinuation), (4) BMI group (<30.0 kg/m^2, 30-39.9 kg/m^2, >40.0kg/m^2, and (5) EDSS score at enrollment above or below the median.

The primary outcome measure is PIRA, dichotomized as present or not, as measured by the rater-determined composite functional outcomes score. This includes the EDSS score with contributions by the 9-hole peg test, SDMT, and 25-foot walking test, and will be constructed as presented in the ORATORIO trial for Ocrelizumab in primary progressive MS vs. placebo.

EDSS will be measured pre-GLP-1 (enrollment) and at the participant's end of study (i.e. one of (a) the end of planned study enrollment period, (b) administrative withdrawal, or (c) participant withdrawal). A positive change in EDSS score of 1.0 points with a baseline EDSS of <5.0 or a positive change in EDSS score of 0.5 points or more with a baseline EDSS score of 5.0 or higher will be considered PIRA. EDSS will be captured at each study visit but the first and last EDSS scores will contribute to the assessment of PIRA for the primary study outcome's hypothesis testing. The use of the EDSS scores at each q24week study visit will also be used in a generalized linear model to determine disability level worsening at any timepoint.

Variables that will be collected or measured, as potentially related to the endpoints of interest, include: subtype of MS (relapsing remitting, primary progressive, secondary progressive), prior DMT use (number of prior DMTs, names), history of relapse of MS in the prior 1 year, highest body weight in the prior year, average body weight in the preceding year, comorbid diagnoses (diabetes mellitus, cardiovascular diagnoses, psychiatric (present/absent, duration)), concomitant medications (particularly those that may affect body weight), smoking status (cigarette), alcohol intake (amount), etc.

Regression variables of interest for the outcome of PIRA will be assessed using exploratory univariate regressions of individual variables of interest. These variables will be determined *a priori* and include sex assigned at birth, age at baseline, BMI at baseline, EDSS at baseline, duration of MS disease (from diagnosis), duration of Ocrelizumab (Ocrevus) treatment.

Secondary endpoints will include (1) a change in 25-foot timed walk, (2) MS-QOL-54 scores, and (3) neurofilament light chain levels.

Sample size justification: The proportion of people with PIRA on GLP-1 agonist drugs and Ocrelizumab is unknown. The proportion of patients with PIRA in relapsing MS ranges up to 24% in published reports.[14] In this study, the detectable difference between a known proportion of patients with PIRA and our study group is >=10%, with alpha=0.05 and power=0.8. Since participants will not be randomized to no treatment or intentionally discontinued on GLP-1 agonist treatment during the study, there is no comparison group.

All approved data storage platforms, back-up and recovery procedures, and data access controls will be performed in accordance with the data storage policy at Feinberg School of Medicine: https://www.feinberg.northwestern.edu/it/policies/file-storage.html

Provisions to protect the privacy interests of participants:

All efforts will be made to ensure participant privacy during the conduct of this study. The minimum necessary information will be shared with each of the study team members. Data will be collected via secure, password-protected, institutionally approved software, both by the study investigators and when participants self-report data. Computers that have appropriate password and anti-virus protections will be used for secure data storage. Privacy protections will include additional safe practices for the storage of any study samples and personal information during payment processes. Participants will be informed through the consent procedures and throughout the study about the privacy of their data. All data will be reported in aggregate on outcomes of interest and outliers in any variable (e.g. age) will not be specifically reported to ensure confidentiality of individual participants who contribute data.

Compensation for research-related injury:
This study is anticipated to incur no more than minimal risk to participants and no more risk than occurs with usual care and treatment of already U.S. FDA-approved medications for their approved indications.

Economic Burden to Participants:
Participants will be compensated for their time in the study, including screening and follow up visits. This payment is considered reimbursement for time. Additional costs for parking or transit will also be provided to ensure all potential participants are included and no one opts out of the study or follow up visits due to financial reasons alone. The study drugs – namely Ocrelizumab and the GLP-1 agonist – will both be paid through the patient's usual health care. *The study will not provide the drug or payment for the drug for either the Ocrelizumab or the GLP-1 agonist to the participant.*

Study Timeline
The submission of ethics board approvals will take approximately 4 months and will be submitted by no later than June 30, 2025. The anticipated start date of the study will be September 15, 2025. Recruitment processes for both study participant groups (Aims 1 and 2) will occur simultaneously. The first patient in for Aim 1 is anticipated within 30 days and the first in for aim 2 is anticipated within 60 days of study start. Recruitment will continue until the target participant enrollment number is reached in both study groups. The enrollment pace will be set not to exceed 6 people per month for Aim 1 to ensure study procedures are robust, with a target of 4-6 people per month. Aim 1 will take approximately 12-15 months to enroll. The anticipated time to complete the enrollment of Aim 1 is December 31, 2026. Aim 2 will take an estimated 12 (up to 18) months to enroll with an anticipated enrollment of 3-4 participants per month. Aim

2 will also complete enrollment in approximately December 2026. Each participant will be followed for 72 weeks. It is anticipated that the last participant out (Aim 2, and complete study) will be April 2028. The final data cleaning and analysis will take approximately 4 months. Interim results will be available to the sponsor at defined intervals before the final study report, at approximately every 6-month intervals. The final study results will be compiled into reports and manuscripts by spring 2028 with study closure in approximately summer 2028.

Qualifications to Conduct Research and Resources Available

The Principal Investigator is a board-certified neurologist with a PhD in International Health Epidemiology. She has over 11 years of experience in neuroimmunology and has served as the lead investigator on multiple clinical trials and observational studies focused on multiple sclerosis.

The research team includes trained clinical research staff who have completed all required certifications, including Good Clinical Practice (GCP), CITI Program training, and other protocol-specific qualifications relevant to this study. All study personnel will receive thorough training on the study protocol, the informed consent process, and ethical considerations to ensure the safety of the participants.

Outpatient clinical facilities at Northwestern Memorial Hospital will be made available to the team as needed to support study-related activities. Biological specimens will be processed using the institution's laboratory infrastructure made available through Northwestern.

SAFETY REPORTING OF ADVERSE EVENTS

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Multiple sclerosis that were not present prior to the AE reporting period.

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).

- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).

- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).

- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which AEs and SAEs as described in section J, "Exchange of Single Case Reports with Genentech," where the patient has been exposed to Genentech product must be reported - reporting period begins after informed consent is obtained and initiation of any study procedures and ends 24 weeks following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment per the section, "Post-Study Adverse Events".

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Ocrelizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech patient Safety during follow up period.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Ocrelizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the Ocrelizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the Ocrelizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the Ocrelizumab or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the Ocrelizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Ocrelizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

ELICITING ADVERSE EVENTS

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

A. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

B. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

C. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

D. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

E. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE version 5.0 will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE Grade Severity

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting selfcare activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE version 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

F. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 24 weeks after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

G. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:

o Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN

o Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

o Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Ocrevus does not have product specific Adverse Events of Special Interest.

H. Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding

- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

I. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

J. Exchange of Single Case Reports with Genentech

Dr. Mateen will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs) (related and not related to the product), pregnancy reports, other Special Situation reports, Non-Serious AESIs, Product Complaints (with or without an AE) where the patient has been exposed to the Product.

It is understood and agreed that Dr. Mateen will perform adequate due diligence with regard to obtaining follow-up information on incomplete case safety reports.

In addition, reasonable attempts must be made to obtain and submit the age or age group of the patient in order to be able to identify potential safety signals specific to a particular population.

Dr. Mateen agrees to allow requests for follow-up information from Genentech, for instance, in order to fulfill regulatory obligations, or where the requested information is not already routinely covered by standard follow-up activities (e.g. clarification of data discrepancies, or to request typical confirmatory laboratory data or batch numbers for biologics and other advanced therapies). Genentech will not contact the reporter directly for such data, but will route all such requests for follow-up to the provided Dr. Mateen contact.

Transmission of these reports (initial and follow-up) will be either electronically via email or by fax to the following email address/fax number:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

Product Complaints without an AE

All Product Complaints without an AE should be reported via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

The completed MedWatch form should be sent to the Genentech contact specified above to report applicable events.

Regardless of the method used, the Batch ID/lot ID for biologics associated with AE/Special Situation/Scenario/PC/AESI must be included.

Reporting Timeline for Applicable Events

Transmission of the applicable event reports (initial and follow-up) will be sent within the timelines specified below:

Type of Report	**Timelines**
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

K. Case Transmission Verification of Single Case Reports

The Parties will verify that all Single Case Report(s) have been adequately received by Genentech, via the exchange of a quarterly. Line Listing that includes all fields detailed in Appendix 2: Content Required in the CTV Line Listing, documenting Single Case Report(s) sent by Dr. Mateen to Genentech in the preceding quarter. The quarterly Line Listing will be exchanged within seven (7) Calendar days of the end of the agreed period. Following CTV, Single Case Report(s) which have not been received by Genentech shall be forwarded by Dr. Mateen to Genentech within five (5) Calendar days from the request.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

Quarterly line-listings and cumulative/final CTV should be sent to ctvistsa@gene.com.

L. MedWatch 3500a Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

Protocol number and title description

Description of event, severity, treatment, and outcome if known

Supportive laboratory results and diagnostics (Section B.6)

Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up

- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

M. Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech, as the Marketing Authorization Holder, will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Dr. Mateen will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Dr. Mateen will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB), where applicable.

N. Reporting Requirements for Adverse Events Originating from Patient Reported Outcomes (PRO)

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

O. Aggregate Reports and Safety Information

Dr. Mateen will be responsible for the distribution of safety information to Site IRB:

Arthur Rubloff Building, 7th Floor
750 N. Lake Shore Dr.
Chicago, IL 60611
Phone 312-503-9338

email: irb@northwestern.edu

For questions related to safety reporting, please contact Genentech Patient Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

All summary reports submitted by the Sponsor-investigator to any health authority should also be sent to Genentech. Copies of such reports, as described below, should be emailed to Genentech at: ctvistsa@gene.com

Dr. Mateen will forward a copy of the Final Study Report to Genentech upon completion of the Study.

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Ocrelizumab-iis-d@gene.com

And to Genentech Patient Safety CTV oversight mailbox at: ctvistsa@gene.com.

Queries

Queries related to the Study will be answered by Dr. Mateen. However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product.

Dr. Mateen agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Dr. Mateen, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Dr. Mateen issues safety communication relevant for Genentech (i.e., a safety issue that notably impacts on the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Dr. Mateen with signal and risk management activities related to the Product within the Study.

Genentech will also provide Dr. Mateen with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

Compliance With Pharmacovigilance Agreement / Audit

The Parties shall follow their own procedures for adherence to single case reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding single case report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding single case reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue. In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

APPENDIX 1: Safety Reporting Fax Cover Sheet

SAFETY REPORTING FAX COVER SHEET - Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]
Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Patient Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX 2: Content Required in the CTV Line Listing

The following fields must be populated by Dr. Mateen in the CTV Line-Listing and sent to Genentech in an agreed format (e.g., Excel):

- CTV Period
- Product name
- Protocol/Program number (if applicable)
- Patient number/other identifier
- Sponsor reference number of case
- Submission date to Genentech
- Patient initials, as applicable

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