PROTOCOL

STUDY TITLE:	Evaluating the Efficacy and Safety of Transitioning Patients from Natalizumab to Ocrelizumab (OCTAVE).
STUDY DRUG:	OCREVUS (ocrelizumab)
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1. INTRODUCTION

Natalizumab (NTZ) is an extremely effective medication in reducing relapses and delaying or reducing sustained disability worsening[i]. Therefore, NTZ is frequently prescribed in relapsing multiple sclerosis (MS) patients with highly active disease who have failed previous disease modifying therapy (DMT). However, there is increased risk of developing progressive multifocal leukoencephalopathy (PML) in patients infected with John Cunningham virus (JCV) who are being treated with NTZ[ii]. Unfortunately, the prevalence of antibodies to the JCV is relatively high, greater than 50 percent of the population[iii]. The risk of developing PML reduces NTZ use, particularly after 2 years of NTZ exposure when the risk of PML increases[iv]. Currently, the risk of developing PML is 4.22 per 1000[v]. Therefore, NTZ is frequently stopped once a patient demonstrates evidence of JCV exposure by the presence of anti-JCV antibodies. However, the risk of disease progression has been reported to be higher when switching to another disease modifying therapy. In a study of 88 patients who had been treated on NTZ for 2 years were either maintained on NTZ, switched to another DMT, or remained off DMT. The relapse rate was 3.7% in the NTZ group verses 17.8% in the group on another DMT[vi]. In another trial evaluating transitioning patients to dimethyl fumarate, the risk of relapse was 19.6% at one year.[vii] Most recently, a multi-center trial was conducted in Sweden evaluating patients switching to rituximab or fingolimod after treatment with NTZ for greater than 6 months. Within 18 months of stopping NTZ, the relapse rate was 17.6% for fingolimod and only 1.8% for rituximab[viii].

In addition, there is no consensus on when to restart another disease modifying therapy although evidence suggests beginning treatment within 3 months of the last dose of NTZ[ix]. Unfortunately, several studies have indicated that approximately a third of patients, within 3-6 months after withdrawal from NTZ, experienced a clinical and/or radiographic relapse[x].

Ocrelizumab (OCR), a humanized monoclonal antibody that selectively binds to, and destroys CD20-expressing lymphocytes (B-cell lymphocytes), has demonstrated robust efficacy in reducing relapse rate with a relative reduction of 46% and 47% respectively in OPERA I and II[xi]. In addition, OCR treatment compared to interferon-β1a therapy led to a significant reduction in contrast enhancing lesions on MRI especially at 24 weeks, 48 weeks, and 96 weeks of treatment with a relative reduction of 94% and 95% respectively. Disability progression at 12 and 24 weeks were also significantly different between both groups with a relative reduction of 40% at 96 weeks. No evidence of disease activity (NEDA) was present in 48% of patients at 96 weeks. The percentage of patients meeting NEDA in the AFFIRM trial was only 37%[xii]. Also, the number was more impressive for OCR with 72% of patients meeting NEDA when assessed after 24 weeks[xiii].

In OPERA I and II, adverse events were the same between the two groups. Not surprisingly, infusion related reactions were more common with 11 patients stopping OCR. Also, in patients receiving OCR, upper respiratory infections and nasopharyngitis were more common. However, unlike NTZ, OCR use has not been associated with the risk of developing PML in patients with MS. Also, to date, there are no reported cases of PML in patients who have received rituximab for the treatment of MS.

The robust therapeutic efficacy of OCR in the phase III pivotal trials, the absence of evidence of PML risk, and the convenience of fewer infusions, makes it an attractive alternative therapy for patients with MS being treated with NTZ, particularly those with the presence of anti-JCV antibodies. However, patients who are JCV negative will likely also be interested in OCR given the potential risk of a false negative to the JCV virus with the reported rate of sero-conversion at 2 to 3 percent per year[xiv].

Given the efficacy and safety data demonstrated in these trials, OPERA I and II, we anticipate that physicians and patients with relapsing MS being treated with NTZ independent of the JCV status would be interested in transitioning to OCR.

However, breakthrough disease is well documented in patients electively coming off NTZ to reduce PML risk. Therefore, conducting a study to determine if patients on NTZ regardless of their JCV status can be transitioned to OCR safely without disease progression is vital.

On March 28, 2017, Roche/Genentech announced FDA approval of OCREVUS ® (Ocrelizumab) for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the efficacy of OCR in RMS patients who have been previously treated with NTZ by evaluating relapse rate, progression on MRI and disability progression.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to assess the effect of OCR on quality of life at months 6 and 12 using Multiple Sclerosis Impact Scale (MSIS-29) and to assess safety and tolerability of OCR in patients previously treated with NTZ by evaluating adverse events and discontinuation.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter, prospective, open-label Phase IV clinical trial. Patients with relapsing forms of MS, ages 18 to 65, who have received a stable dose of NTZ for 12 or more consecutive months, and have been free of relapses, disability worsening or MRI progression 6 months prior to the transition screening visit will be eligible for the study. After informed consent to participate has been obtained, the patient will have a neurological exam, EDSS, 3T or 1.5T MRI, MSIS-29 and labs done for the screening visit to determine eligibility. 3T or 1.5T brain MRI with and without contrast will be performed with the standard MS protocol. It is preferred that the MRIs are done on a 3T scanner for this trial, but not required. MRIs will be performed with 3mm slice thickness with no gaps between slices. Patients will receive their first dose of OCR 4 to 6 weeks after the last dose of NTZ. Other baseline measures, including EDSS, MSIS-29, and labs will be performed within 4 weeks of screening. A neurological exam, EDSS, and labs will be performed at month 3, month 6, month 9, and month 12. MSIS-29 will be performed at months 6 and 12. MRIs will be performed at screening to determine

eligibility and at months 3, 6, and 12. All adverse events will be reported to the study sponsor. OCR will not be provided by the study; the medication will be supplied through the patient's commercial pharmacy and billed to the patient or the patient's insurance.

Patients will receive OCR 4-6 weeks after their last infusion of NTZ. OCR 300mg IV will be given on Day 0 and repeated with the same dose on Day 14±2. Patients will then receive OCR 600mg IV every 24 weeks.

If discontinuation of study drug occurs, the subject may continue in the trial for observational purposes. If willing to continue, they will complete all visit items moving forward, with the exception of study drug dosing and pregnancy testing (if applicable). If study drug is discontinued and the subject is unwilling to continue in the trial, a premature termination visit will be completed as soon as possible.

The target enrollment is 50 patients from 5 centers. Serious adverse events recorded during the trial will be reported to the study sponsor via Medwatch form.

3.2 RATIONALE FOR STUDY DESIGN

The clinical data from OPERA I and II demonstrated a highly efficacious medication with a significant reduction in relapses, MRI progression, and disability progression. In addition, the data suggest that OCR is well tolerated as only 3.2% of patients withdrew secondary to side effects in OPERA I and 3.8% of patients withdrew in OPERA II. From a safety perspective, no opportunistic infections were seen in the clinical trials, and this includes PML.

NTZ is a highly effective medication for treating patients with relapsing MS. However, despite adequate disease control and JCV status, patients will eventually discontinue secondary to the potential risk of PML[xv]. Unfortunately, multiple studies have demonstrated an increase in risk of disease progression after switching to another agent after discontinuing NTZ[xvi],[xvii],[xviii]. So, given the robust clinical data and safety profile from the pivotal OCR trials, this medication is an attractive option for patients and clinicians.

In this clinical trial, patients will receive the FDA approved dose and frequency of OCR. In the RESTORE trial, NTZ concentrations reached undetectable levels 8 weeks after the last infusion. Also, data from several clinical trials including STRATEGY and SWITCH suggest that a shorter washout period will reduce the risk of disease recurrence[xix]. Therefore, OCR will be infused at a minimum of 4 weeks after the last dose of NTZ and up until 6 weeks.

Measuring breakthrough disease to date is best evaluated by measuring clinical and radiographic changes. A patient outcome measure, MSIS-29, will help evaluate changes in quality of life after transitioning to OCR.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

The primary endpoint is the proportion of relapse-free patients at month 12 after switching from NTZ to OCR.

Relapse is defined as:

- Occurrence of new or worsening neurological symptoms attributable to MS
- Symptoms persisting for > 24 hours
- Symptoms not attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reaction to medication)
- Symptoms immediately preceded by a stable or improving neurological state for at least 30 days
- Symptoms accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate FSS, or 1 point on 2 or more of the appropriate FSS; the change has to affect the selected FSS (i.e. pyramidal, ambulation, cerebellar, brainstem, sensory, or visual)

3.3.2 Secondary Outcome Measures

- Proportion of relapse free patients at months 3, 6, and 9
- Annualized Relapse Rate (ARR)
- Mean time to first relapse on OCR
- Proportion of patients free from MRI evidence of MS disease activity at months 3, 6, and 12
- Proportion of patients with new or enlarging T2 lesions at 3, 6, and 12 months. For patients with new or enlarging lesions, the number of new and enlarging lesions
- Proportion of patients with new Gd+ lesions at months 3, 6, and 12. For patients with new Gd+ lesions, number of new Gd+ lesions detected at months 3, 6, and 12.
- Change in the EDSS score from baseline to month 12.
- Change in MSIS-29 from baseline to months 6 and 12
- Number and type of AEs and SAEs
- Proportion of patients that discontinued OCR

3.3.3 Ancillary Safety Outcome Measures

- Number and type of infusion related reactions based on dose including the severity of the reactions
- Number of and type of infections during the trial.

3.4 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.5 and Appendix A, Study Flowchart).

A full neurologic examination will be conducted at every visit (may be historical at screening if an exam was completed within 28 days prior to consent, and may be waived at baseline if screening and baseline are 7 or less days apart). Any worsening or new abnormality (including laboratory results) that is determined by the investigator as clinically significant will be recorded as an AE and will be monitored until resolution or stabilization. MS related symptoms are not to be reported as AEs unless, in the opinion of the investigator, the symptoms are unusually serious and relevant.

The recommendation from the OCR prescribing information dated 11/2018 is to pre-medicate with 100mg of methylprednisolone (or an equivalent corticosteroid) administered intravenously approximately 30 minutes prior to each OCR infusion to reduce the frequency and severity of infusion related reactions (IRRs) [see Warnings and Precautions (5.1) in prescribing information]. Also, it is recommended to pre-medicate with an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes prior to each OCR infusion to further reduce the frequency and severity of infusion reactions.

Recommended medications to be available if there is an infusion reaction (per treating investigator discretion):

A. Epinephrine – anaphylaxis
B. Albuterol – bronchospasm or hypoxia
C. Famotidine 20mg IV – hives, itching, or anaphylaxis
D. Oxygen therapy – shortness of breath, chest pain, or hypoxia
E. Acetaminophen – pain, fever, and headaches
F. Methylprednisolone – hives, itching, shortness of breath, or anaphylaxis

Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

Pre-medications, infusion reaction management, and infusion reaction medications are to be left to treating investigator discretion.

<u>Suggested Management of IRRs</u>

Severe IRRs
If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. The infusion should be re-started only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.

Mild-Moderate IRRs
If the event that a patient experiences is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current ICH GCP Guidelines and the Code of Federal Regulations for clinical research. Any amendment to the study protocol must approved by Providence IRB and the IRB or Ethics Committee of each site before implementation. AEs and protocol deviations must be reported according to the guideline of the IRB or Ethics Committee of each study site.

4.0 MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

Subject selection will be based on meeting all of the required inclusion and exclusion criteria to be eligible to participate in the trial. Subjects are eligible to participate regardless of their JCV status.

4.1.2 Inclusion Criteria

1. Male or female with relapsing form of MS, age 18 to 65, inclusive, at the time of informed consent.
2. In the opinion of the investigator, able to understand the purpose, risks, and responsibilities of the study and provide signed informed consent document.
3. Must have received a stable dose of NTZ for 12 or more consecutive months, and have had no evidence of on-NTZ disease activity (clinically or on MRI) for the 6 months prior to the screening visit.
4. Naïve to OCR.
5. No evidence, in the opinion of the investigators of significant cognitive limitation or psychiatric disorder that would interfere with the conduct of the study.
6. EDSS of ≤ 6.0 at screening.
7. Female patients of childbearing potential must practice effective contraception and continue contraception during the study.

4.1.3 Exclusion Criteria

1. History of primary or secondary progressive multiple sclerosis.
2. Evidence of active hepatitis B infection at screening.
3. Any mental condition of such that patient is unable to understand the nature, scope, and possible consequences of the study.
4. Patients with untreated hepatitis C or tuberculosis. Patients who have history of PML or known to be HIV positive, per standard care.
5. Any persistent or severe infection.
6. Pregnancy or lactation.

7. Significant, uncontrolled somatic disease or severe depression in the last year.

8. Inability to complete an MRI.

9. Previous treatment with B-cell targeted therapies.

10. Current use of immunosuppressive medication.

11. Patients who have had evidence of disease activity within the 6 months prior to screening. This includes MS relapse, or new or enlarging T2 lesions or Gd+ enhancing lesions, or disability progression.

12. Patients with any significant comorbidity that in the opinion of the investigator, would interfere with participation in the study.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an observational study in patients who will receive OCR as part of their standard care.

4.3. STUDY TREATMENT

Patients will be initiated on OCR after informed consent and screening assessment have been completed. The first dose of OCR will be administered between 4 and 6 weeks after the last dose of NTZ. OCR will be prescribed by patient's neurologist as standard of care and paid for by the patient/patient's insurance.

4.3.1 Dosage, Preparation, Administration and Storage

Ocrelizumab Formulation Packaging, and Handling

The following requirements are listed in the OCR prescribing information dated 11/2018 and are to be followed as part of the standard of care preparation of OCR for infusion. The study team is not responsible for collecting or reviewing data on how the drug was packaged, prepared, handled, or stored for the purposes of this trial.

Ocrelizumab will be supplied by the commercial pharmacy in a liquid formulation containing 30-mg/mL ocrelizumab in 20mM sodium acetate at pH 5.3, with 4% trehalose dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I USP, glass vial fitted with a 20-mm, fluoro-resin, laminated stopper and an aluminum seal with a flip-off plastic cap and contains a nominal 300 mg ocrelizumab. No preservative is used as each vial is designed for single use.

The ocrelizumab drug product must be diluted before administration. Solutions of ocrelizumab for IV administration are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride to a final drug concentration of 1 to 2 mg/mL.

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter.

The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 micrometer).

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2−8°C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2−8°C. Infusion solution must be completely administered to the patient within 32 hours of preparation (not exceeding 24 hours at 2−8°C and 8 hours at room temperature). In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

Dosage, Administration, and Compliance

Ocrelizumab 300mg IV will be given on Day 0 and repeated with the same dose on Day 14±2. Patients will then receive ocrelizumab 600mg IV every 24 weeks. Medication will not be provided by the study.

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member.

See section 3.4 for recommended pre-medications and recommended medications to treat IRRs. For the 300-mg dose, each ocrelizumab infusion should be given as an IV infusion over approximately 150 minutes (2.5 hours). For the 600-mg dose, each ocrelizumab infusion should be given as an IV infusion over approximately 215 minutes (3.5 hours).Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.

Ocrelizumab must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to control the infusion rate, and ocrelizumab should be infused through a dedicated line. It is important not to use evacuated glass containers (to prepare the infusion), which require vented administration sets, because this causes foaming as air bubbles pass through the solution.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed and the patient may be discharged.

See the OCR prescribing information dated 11/2018 for detailed instructions on drug preparation, storage, and administration.

4.3.2 Dosage Modification

Dose modification of OCR is not permitted.

4.3.3 Overdose

There have been no observed overdoses in human clinical trials.

4.4 CONCOMITANT AND EXCLUDED THERAPY

All concomitant medications are allowed except immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers while patients are receiving OCR. All medications including over-the-counter medication and supplements will be recorded at each clinical visit. At screening, all medications taken 4 weeks prior to screening will be reviewed and recorded, as well as all prior lifetime MS disease modifying therapies taken by the patient.

4.5 STUDY ASSESSMENTS

The investigator or designated research staff will obtain informed consent from each patient after explaining the purpose of the study and the potential risks and benefits known or can be reasonably expected. The IRB approved informed consent will be signed by the patient before any screening assessments or procedures are performed.

4.5.1 Assessments during Treatment

Visit 1/Screening Visit (-28 to -1 days prior to Baseline Day 0)

The following clinical and laboratory evaluations will occur within 28 days prior to Baseline (Day 0 OCR dose), unless otherwise noted. The investigator or designee must perform all screening evaluations to determine patient eligibility.

- Informed consent
- Eligibility review
- Demographic information
- Review of disease and medical history
- Review of prior and concomitant medications, including lifetime MS treatment history
- JC Virus Status and date of testing
- Reason(s) for switching to Ocrelizumab
- Vital signs
- Neurological exam (may be historical exam if completed within 28 days prior to consent)
- Relapse assessment (may be historical assessment if completed within 28 days prior to consent)
- Confirmation of estimated EDSS of 0 to 6, inclusive (If Screening is within 7 days prior to Baseline and a full EDSS was conducted at Screening, the EDSS is no longer required at the Baseline visit)
- Laboratory assessments:
    - CBC, CMP, and urine pregnancy test (female only) (may be historical laboratories if completed within 28 days prior to consent)
    - Hepatitis B testing (may be historical laboratories if completed within 6 months prior to consent)
- MRI (may be historical if completed within 6 weeks prior to Baseline (Day 0), recommended to be completed after last dose of NTZ. Must be completed prior first dose of OCR at Day 0)

Visit 2/Baseline Visit (Day -7 to Day 0)

The following clinical and laboratory evaluations will occur at baseline visit. The investigator or designee will review inclusion/exclusion criteria to confirm patient eligibility. Day 0 is defined as the day of OCR administration.

- Vital signs (not required if Baseline is within 7 days of Screening visit)

- Eligibility review
- Neurological exam (not required if Baseline is within 7 days of Screening visit)
- Relapse assessment (not required if Baseline is within 7 days of Screening visit)
- EDSS (not required if Baseline is within 7 days of Screening and a full EDSS was collected at Screening).
- MSIS-29 (if Baseline is within 7 days of Screening visit, may be collected at Screening instead of baseline visit).
- Laboratory assessments: CBC, CMP, Pregnancy test (female only) (not required if Baseline is within 7 days of Screening visit, but pregnancy test must be done if Screening Visit test was historical)
- Concomitant medications and adverse events (not required to be reviewed with the patient in person if Baseline is within 7 days of Screening visit, collect via chart review)
- OCR administration (300mg, 2 administrations: Day 0 and Day 14 ± 2 days)

Visit 3/3 Month Visit (Day 84 +/- 14 days from Baseline Day 0)

The following clinical and laboratory evaluations will occur 84 days from Baseline with a +/- 14 day window.

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- Laboratory assessments: CBC, CMP, Pregnancy test (female only)
- MRI
- Concomitant medications and adverse events

Visit 4/6 Month Visit (Day 168 +/- 14 days from Baseline Day 0)

The following clinical and laboratory evaluations will occur 168 days from Baseline with a +/- 14 day window.

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- MSIS-29
- Laboratory assessments: CBC, CMP, Pregnancy test (female only)
- MRI
- Concomitant medications and adverse events
- OCR administration (600mg)

Visit 5/9 Month Visit (Day 252 +/- 14 days from Baseline Day 0)

The following clinical and laboratory evaluations will occur 252 days from Baseline with a +/- 14 day window.

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- Laboratory assessments: CBC, CMP, Pregnancy test (female only)
- Concomitant medications and adverse events

Visit 6/12 Month Visit (Day 336 +/- 14 days from Baseline Day 0)

The following clinical and laboratory evaluations will occur 336 days from Baseline with a +/- 14 day window.

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- MSIS-29
- Laboratory assessments: CBC, CMP, Pregnancy test (female only)
- MRI
- Concomitant medications and adverse events
- OCR administration (600mg)

End of Study (EOS) Phone Contact (30 days +/- 14 days from study discontinuation)

The following clinical evaluation will occur 30 days +/- 14 days from study completion (12 Month OCR administration) or premature termination visit:

- Adverse events

Premature Termination Visit

If study drug is withdrawn and the patient is unwilling to continue in the trial for observation, complete a premature termination visit as soon as possible. If the patient discontinues from the study for any other reason noted in the subject discontinuation criteria, a premature termination visit must be performed as soon as possible. Patients who were withdrawn from the study for any reason will not be replaced. The following clinical and laboratory evaluations will be performed:

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- MSIS-29
- Laboratory assessments: CBC, CMP, Pregnancy test (female only)
- Concomitant medications and adverse events
- Primary reason for discontinuation

Unscheduled Visits

Patients will be instructed to contact their treating physician in the event of a relapse and may be asked to return for unscheduled visit to assess any undesired clinical, or laboratory changes that occur during the study.

- Vital signs
- Neurological exam
- Relapse assessment
- EDSS
- Laboratory assessments: CBC, CMP, Pregnancy test (female only) (if indicated, per treating investigator)
- MRI (if indicated, per treating investigator)
- Concomitant medications and adverse events

Study Withdrawal

If a patient is lost to follow-up, she/he will be withdrawn from the study. Appropriate means of contact to consider lost to follow-up are 3 documented phone attempts and 1 certified letter.

4.6 DISCONTINUATION OF THERAPY

OCR therapy must be discontinued for any of the following reasons:

- Life-threatening IRR or serious hypersensitivity reaction
- Active hepatitis B infection
- PML
- Active TB, either new onset or reactivation
- HIV
- Patient becomes pregnant
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)

4.7 SUBJECT DISCONTINUATION

Patients may also be withdrawn from the study for any of the following reasons:

- Patient withdraws consent
- Patient is unwilling or unable to comply with the protocol
- Physician's discretion

4.8 STUDY DISCONTINUATION

Genentech Study Center, and the Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- Patient enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- Study protocol not followed

4.9 STATISTICAL METHODS

4.9.1 Analysis of the Conduct of the Study

The following documentation will be collected and analyzed for all enrolled patients in order to maintain the integrity of the study:

A. Enrollment date and time
B. Demographic information
C. Baseline disease status
D. If applicable, protocol violation date and cause
E. If applicable, discontinuation date and cause

Demographic information and baseline disease for all enrolled patients, those who violated protocol, and those who discontinued will be summarized and reported separately. The reasons for discontinuing or violating protocol and the patient's time on drug at occurrence will be reported and any influence on the trial results will be discussed. To assess the comparability between centers, summaries will be reported for all patients overall and by study center. Any other irregularities that result in missing data will be fully identified and discussed.

All patients that followed protocol will be used to evaluate efficacy, safety, and tolerability. This includes patients that discontinued but followed protocol up to discontinuation.

4.9.2 Analysis of Treatment Group Comparability

Not applicable

4.9.3 Efficacy Analysis

a. Primary Endpoint

Proportion of patients relapse free at 12 months after switching from NTZ to OCR

b. Secondary Endpoints

- Proportion of patients relapse-free at 3, 6, and 9 months after switching to OCR
- Mean time to first relapse
- MRI evidence of MS disease activity
- Proportion of patients with New or Enlarging T2 lesions at 3, 6, and 12 months. For patients with New or Enlarging T2 lesions, number of New and Enlarging T2 lesions.
- Proportion of patients with New Gd+ lesions detected at months 3, 6, and 12. For patients with New Gd+ lesions, number of New Gd+ lesions
- Annualized relapse rate (ARR)
- Change in EDSS from baseline to 12 months
- Change in MSIS-29 from baseline to 6 and 12 months

All patients that followed protocol will be used to evaluate the proportion of patients relapse-free at 3, 6, 9, and 12 months, mean time to first relapse, and ARR. This includes those that discontinued early but followed protocol up to discontinuation. All patients that followed protocol and did not discontinue will be used to evaluate MRI

evidence of MS disease activity at 3, 6, and 12 months, the change in MSIS-29 from baseline to 6 and 12 months, and the change in EDSS from baseline to 12 months.

A full analysis set consistent with the intent-to-treat (ITT) principle will also be used to analyze the proportion of patients relapse-free at 3, 6, 9, and 12 months, mean time to first relapse, and ARR using all subjects. Subjects who entered the trial and did not meet inclusion criteria may be excluded.

Summary statistics will be presented for continuous variables (mean, standard deviation, median, range) and categorical variables (counts and percentages). All analyses will use two-sided confidence intervals and p-values at the 0.05 significance level.

Primary Analysis

Kaplan-Meier survival analysis methodology will be used to determine the proportion of patients relapse-free at months 3, 6, 9, and 12. Median and mean time to first relapse with confidence intervals will be reported. Log rank tests and graphical presentations of Kaplan Meier curves with confidence intervals will be used to examine effects of center, gender, categorized age, categorized EDSS and duration of disease on survival distribution.

Secondary Analysis

ARR will be analyzed with a Poisson or negative binomial analysis with the total number of relapses as a dependent variable and the logarithm of time followed as an offset. The number of new or enlarging T2 and Gd+ lesions at 3, 6, 9, and 12 months will be summarized and reported. The mean and median change in EDSS from baseline will be determined at 12 months and tested by Wilcoxon signed-rank tests. The mean and median change in MSIS-29 from baseline will be determined at 6 and 12 months and tested by Wilcoxon signed-rank tests.

4.9.4 Safety Analysis

Information on the timing, severity, relationship to drug, relationship to therapy, effect on therapy, and degree of seriousness of adverse events will be collected from and summarized for all patients.

4.9.5 Missing Data

Demographic information and baseline disease for patients who followed protocol and completed the study, violated protocol, and discontinued the study will be reported separately and compared. The reasons for discontinuing or violating protocol and the patient's time on drug at occurrence will be reported and any influence on the trial results will be discussed. To assess the comparability between centers, summaries will be reported for all patients overall and by study center. Any other irregularities that result in missing data will be fully identified and discussed.

For the per protocol and full analysis sets, missing data due to discontinuation will be incorporated as censored time points in the survival analysis of relapse-free patients and ARR will be calculated using the range of time that the individual was in the study. If interim time points at 3, 6, or 9 months are missing, only the time points available will be used in the survival analysis. No relapse data will be missing at baseline, since only patients relapse free for six months are included. For the Kaplan Meier analyses and

log rank tests stratified by age, gender, EDSS, and center, we expect these patient characteristics to be non-missing. However, if they are missing, a complete case analysis per variable will be used and the number of missing will be reported.

For the analysis of the change in EDSS and MSIS-29, a complete case analysis with per protocol patients will be used.

4.9.6 Determination of Sample Size

The sample size was based on a Kaplan Meier analysis with proportion of patients relapse free at 12 months as the primary endpoint. Assuming a relapse-free proportion of 0.80 at 12 months, 45 patients are required to say that the relapse free proportion is no lower than 0.68, with 95% confidence. To account for 10% attrition, a total of 50 patients are needed.

4.10 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. REPORTING OF ADVERSE EVENTS

An AE is an unfavorable unintended sign, symptom, or disease that is experienced by the patient, whether or not there is a causal relationship with OCR. At the time of consenting, each patient will be given the names and telephone numbers of the study personnel for reporting AE's. The investigator must conduct thorough assessment to determine the severity of the AE and the relationship to the study drug. Any clinically significant AE of severity moderate or higher, requires follow up until resolution or stabilization by the treating investigator beyond the end of study contact.

All AEs should be recorded in the patient's AE case report form regardless of severity or relationship to the study drug. The investigator must review the laboratory findings for significance (all out of range values must be assessed as clinically significant or not clinically significant) and sign and date the laboratory report. All clinically significant laboratory findings must be reported as adverse events.

Any severe laboratory abnormalities that are considered serious should be reported to the coordinating center as outlined below.

All SAEs must be reported by the investigator to Genentech by email usds_aereporting-d@gene.com or fax (650) 238-6067 and Providence Regional Research Regulatory Office by email suzanne.balleisen@providence.org (Regulatory) and CC tiffany.gervasi@providence.org (Study Manager) or fax to 503-215-6547 (Regulatory) and (503) 216-1039 (Study Manager) within 24 hours of the investigator's knowledge of the event.

Severity

The intensity of severity of an AE will be graded as follows:

Mild — Symptoms(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms(s) but may be given because of personality of subject

Moderate — Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.

Severe — Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with investigational drug; treatment for symptom(s) may be given and/or subject hospitalized.

Relationship to Study Drug

The relationship or association of the AE to a study drug will be characterized as follows:

Not related — Any event that does not follow a reasonable temporal sequence from administration of investigational drug *AND* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Unlikely — Any event that does not follow a reasonable temporal sequence from administration of investigational drug *OR* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly — Any reaction that follows a reasonable temporal sequence from administration of investigational drug *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Related — Any reaction that follows a reasonable temporal sequence from administration of investigational drug *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

5.1 ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to OCR 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, symptom, 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.

- 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).

5.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

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

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 30 days 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.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through 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 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 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 ocrelizumab; and/or the AE abates or resolves upon discontinuation of ocrelizumab or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than 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., event diagnosed 2 days after first dose of ocrelizumab).

Expected versus unexpected is to be evaluated for SAEs.

Expected adverse events are those adverse events that are listed or characterized in the prescribing information.

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

5.3 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/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 ok 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 5.1.2), 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 (v5.0) will be used for assessing adverse event severity. The 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
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 self-care 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 (v5.0), 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 ocrelizumab or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy

should also occur. 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 ocrelizumab should be reported as an SAE.

Additional information on any ocrelizumab-exposed pregnancy and infant will be requested by Genentech Drug Safety at specific time points (i.e. after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

g. 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 who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety and the Sponsor.

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h. Case Transmission Verification of Single Case Reports

The Sponsor agrees to complete the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by the Sponsor to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Providence Brain and Spine Institute to Genentech within five (5) calendar days from request by Genentech.

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

i. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to OCR, 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.

There are no *ocrelizumab* Events of Special Interest.

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:
    - Treatment-emergent ALT or AST $>$ 3 $\times$ ULN in combination with total bilirubin $>$ 2 $\times$ ULN
    - Treatment-emergent ALT or AST $>$ 3 $\times$ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

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

j. Exchange OF Single Case Reports

Providence Brain and Spine Institute will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above mentioned single case reports adequately to Genentech and the Sponsor within the timelines described below. The completed MedWatch reporting form should be faxed/emailed immediately upon completion to Genentech and the Sponsor at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

Fax: 650-238-6067 *or*
Email: usds_aereporting-d@gene.com

AND

Fax: (503) 215-6547 (Regulatory) and (503) 216-1039 (Study Manager) *or*
Email: suzanne.balleisen@providence.org (Regulatory) and CC tiffany.gervasi@providence.org (Study Manager)

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

AND

Fax: (503) 215-6547 (Regulatory) and (503) 216-1039 (Study Manager) *or*
Email: suzanne.balleisen@providence.org (Regulatory) and CC tiffany.gervasi@providence.org (Study Manager)

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study. These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports, other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product (OCR), will be sent on a MedWatch form to Genentech Drug Safety and to the Sponsor. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **Serious Adverse Drug Reactions (SADRs)**

Serious AE reports that are related to OCR shall be transmitted to Genentech and the Sponsor within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to OCR shall be transmitted to Genentech and the Sponsor within thirty (30) calendar days of the awareness date.

- **AESIs**

AESIs shall be forwarded to Genentech and the Sponsor within fifteen (15) calendar days of the awareness date.

- **Special Situation Reports**

Pregnancy reports

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy where the fetus may have been exposed to OCR, shall be transmitted to Genentech and the Sponsor within thirty (30) calendar days of the awareness date. 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.

- **Other Special Situation Reports**

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech and the Sponsor within thirty (30) calendar days:

  - Data related to OCR 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.

- **Product Complaints**

All Product Complaints (with or without an AE) shall be forwarded to Genentech and the Sponsor within fifteen (15) calendar days of the awareness date.

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.

5.4 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

Reporting to Ethics Committees and Investigators

Providence Brain and Spine Institute will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Providence Brain and Spine Institute will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

And Providence Brain and Spine Institute will be responsible for the distribution of safety information to the IRB of record:

Providence Health & Services Institutional Review Board
5251 NE Glisan St.
Portland, OR 97213
Tel: (503) 215-6512
Fax: (503) 215-6632

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

5.5 AGGREGATE REPORTS

Other Reports

Providence Brain and Spine Institute will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

Study Close-Out
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 Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

5.6 QUERIES

Queries related to the Study will be answered by Providence Brain and Spine Institute. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to OCR. The Sponsor agrees that it shall not answer such queries from regulatory authorities and other sources relating to OCR independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests 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.

5.7 SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which OCR is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to OCR. Providence Brain and Spine Institute agrees that it shall not answer such queries from media and other sources relating to OCR but shall redirect such queries to Genentech/Roche.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Current *curriculum vitae* of the Principal Investigator
- Written documentation of IRB approval of protocol and informed consent document
- A copy of the IRB-approved informed consent document
- A signed Clinical Research Agreement

6.2 INFORMED CONSENT

The informed consent document must be signed by the subject before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

6.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must

also keep the IRB informed of any significant adverse events that meet reporting criteria.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the prescribing information and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., safety amendments and updates, etc.) that meet the IRB reporting requirements.

6.4 STUDY MONITORING REQUIREMENTS

A study specific monitoring plan will be developed according to Providence Internal Monitoring of Study Data SOP to verify the approved protocol is being followed, study data are accurately recorded, and regulatory documents are properly maintained.

6.5 DATA COLLECTION

A secure, password-protected clinical trials management system will be used to collect patient information and study data. The completeness of data and whether the data values are in appropriate ranges will be checked periodically. Investigators or designated personnel will be asked to complete data clarification requests for confirmation of missing data or questionable information.

6.6 STUDY MEDICATION ACCOUNTABILITY (IF APPLICABLE)

Not applicable

6.7 DISCLOSURE AND PUBLICATION OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB for each study site, if appropriate.

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for the publication of study results.

Additionally, Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF) requires Responsible Parties to register and submit summary results of clinical trials with ClinicalTrials.gov. The law applies to certain clinical trials of drugs (including biological products) and medical devices (refer to FDAAA 801 Requirements to learn about Responsible Party, Applicable Clinical Trials, and deadlines for registration and results submission).

6.8 RETENTION OF RECORDS

The records and documents pertaining to the conduct of this study must be retained by the principal investigator for a minimum period of ten (10) years after the study is terminated or completed at all sites. HIPPA and other appropriate legal guidelines regarding privacy and retention of records must also be followed.

APPENDIX A STUDY FLOWCHART

Procedure/Visit	Screening Visit #1 (Day -28 to -1)	Baseline Visit #2 (Day -7 to Day 0)[W]	Month 3 Visit #3 (Day 84 ±14)	Month 6 Visit #4 (Day 168 ±14)	Month 9 Visit #5 (Day 252 ±14)	Month 12 Visit #6 (Day 336 ±14)	EOS Phone Contact[A]	Premature Termination Visit[B]	UNS Visit[C]
Informed Consent	x								
Eligibility Review (INC/EXC)	x[H]	x[I]							
Disease and Medical History	x								
Demographics	x								
Reason(s) for switching to OCR	x								
Vital Signs[S]	x	x[Y]	x	x	x	x		x	x
Neuro Exam[K]	x[U]	x[Y]	x	x	x	x		x	x
Relapse Assessment	x [U]	x[Y]	x	X	x	x		x	x
EDSS	x[T]	x[Y]	x	X	x	x		x	x
MSIS-29[J]		x[Z]		X		x		x	
Metabolic panel	x[U]	x*[Y]	x	x	x	x		x	x[D]
CBC[Q]	x[U]	x*[Y]	x	x	x	x		x	x[D]
Urine preg test[E]	x*[U]	x*[Y]	x*	x*	x*	x*		x*	x*[D]
JCV Antibody Status	x[R]								
Hepatitis B testing	x[V]								
MRI	x[L]		x*	x[M]		x[M]			x[D]
OCR Administration[N]		x[F]		x[G]		x[G]			
Primary Reason for Discontinuation								x	
Con meds	x[O]	x[Y]	x	x	x	x		x	x
Adverse Events		----------Monitor and record AEs at each visit after Screening----------							

*These items are paid for by the study.
A: 30 days ±7 days from study discontinuation (Month 12 OCR Administration or Premature Termination Visit).
B: If study drug is withdrawn and the patient is unwilling to continue in the trial for observation, complete a premature termination visit as soon as possible. If the patient discontinues from the study for any other reason noted in the subject discontinuation criteria, a premature termination visit must be performed as soon as possible.
C: Subjects will be instructed to contact their treating physician in the event of a relapse and may be asked to return for unscheduled visit to assess any undesired clinical, or laboratory changes that occur during the study.
D: To be performed only if indicated, per treating investigator.
E: For female subjects of childbearing potential only. If urine pregnancy test is positive, must be confirmed by serum pregnancy test. Not required at 2nd dose of 300mg OCR.
F: 300mg administered on Day 0, and then again on Day 14±2 days. First dose on Day 0 should be within 4 to 6 weeks of last dose of NTZ.
G: 600mg administration as one infusion.
H: At screening, review all eligibility criteria that are able to be assessed.
I: At baseline, eligibility must be reviewed prior to OCR administration to ensure all screening procedures/results are reviewed and subject meets all entrance criteria.
J: Review results for potential AEs.
K: At Visit #1, report any clinically significant findings as medical history. At all other applicable visits, report clinically significant findings as AEs.
L: May be historical MRI. if completed within 6 weeks prior to Baseline (Day 0). Recommended to be completed after last dose of NTZ.Must be prior to first dose of OCR at Day 0.
M: MRI to be completed and reviewed by investigator prior to OCR administration.
N: Subjects should be informed that they should expect to be at infusion up to one full day for each dose. See section 4.3.1 for pre-medication instructions.
O: At Visit #1, also review all prior medications taken within last 4 weeks and all prior lifetime MS disease modifying therapies.
P: Metabolic Panel to include: Total Bilirubin, ALT, AST,, Urea, Creatinine, , Calcium, Sodium, and Potassium.
Q: CBC to include: Hemoglobin, Hematocrit, RBCs, WBC Absolute and Differential, Absolute Neutrophil Count (ANC), Absolute Lymphocytes, and Quantitative Platelet Count.
R: To include JCV index, status, and date of most recent result. JCV laboratory is not being collected at screening visit.
S: Vitals assessment to include: weight, BP, HR, oral temperature, RR. Height also to be recorded at screening.
T: Full EDSS not required at screening, but investigator must confirm subject's estimated EDSS is not greater than 6 based on the most recent neurologic exam. If screening is within 7 days prior to 1st dose of OCR, a full EDSS must be completed at Screening. Full EDSS will be required at all subsequent visits.
U: Data for this assessment may be collected from historical clinical record if completed within prior 28 days (inclusive) of subject informed consent form signature date. If not available, completed at screening visit.
V: Data for this assessment may be collected from historical clinical record if completed within prior 6 months (inclusive) of subject informed consent form signature date. If not available, completed at screening visit.
W: Day 0 is defined as the day of administration of the 1st dose of OCR. Other Baseline procedures may be completed up to 7 days prior to 1st dose (Day -7 to Day 0).
Y: If Screening visit falls within 7 days prior to 1st dose OCR (Day -7 to Day 0), these procedures do not need to be repeated. Pregnancy test should be done at baseline if historical test used for screening visit.
Z: If Screening visit falls within 7 days prior to 1st dose OCR (Day -7 to Day 0), this assessment may be completed at screening and it does not need to be repeated at Day 0 (day of first OCR infusion).

APPENDIX B

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 238-6067
AE / SAE EMAIL: usds_aereporting-d@gene.com

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	_____ / _____/ _____ (DD/MMM/YY)
Follow-up Report Date	_____ / _____/ _____ (DD/MMM/YY)

Subject Initials (Enter a dash if patient has no middle name)	____ - ____ - ____

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

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