PROTOCOL

STUDY TITLE:	Comparing the Risk and Severity of Infusion-Related Reactions in Patients Premedicated with Cetirizine versus Diphenhydramine Prior to Ocrelizumab Infusions (PRECEPT)
SUPPORT PROVIDED BY:	Genentech, Inc.
INVESTIGATOR:	Kyle Smoot, MD
	9135 SW Barnes Road, Suite 461
	Portland, OR 97225
	Phone – 503.216.1150
	Fax – 503.216.1039
SUB-INVESTIGATORS:	Stanley Cohan, MD, PhD
	Justine Brink, DO, MPH
	Vitalie Lupu, MD, FAAN, MSCS
	Leah Gaedeke, MSN, FNP-BC
INSTITUTION:	Providence Health & Services
	Providence Brain & Spine Institute
	9155 SW Barnes Rd, STE 317, Portland, OR 97225
STUDY NUMBER:	ML41308
PROTOCOL VERSION/DATE:	Version 4.0/19MAY2021

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1. INTRODUCTION

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, sustained disability worsening, and MRI indicators of disease activity in patients with relapsing multiple sclerosis (RMS)[1]. For patients with primary progressive MS (PPMS), OCR demonstrated reduction in disability progression compared to patients receiving the placebo treatment[2]. The medication is well-tolerated with upper respiratory infections being the most common potential side effect followed by infusion-related reactions (IRRs). At least one infusion reaction occurred in 34.3% of the patients in OPERA I and OPERA II[1]. The majority of the infusion reactions were mild to moderate and occurred with the first infusion of dose 1. In the clinical trials, all patients were pre-medicated with 100mg of methylprednisolone, and per the protocol, an analgesic/antipyretic such as acetaminophen and an IV or oral antihistamine such as diphenhydramine 50mg were recommended to use prior to starting OCR to minimize IRRs. However, drowsiness is commonly associated with diphenhydramine; therefore, a newer antihistamine such as cetirizine may be tolerated better without an increase in IRRs.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this pilot study is to evaluate whether there is some evidence that cetirizine is non-inferior to diphenhydramine in limiting the proportion and severity of reactions from OCR infusions.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate patient treatment satisfaction after receiving cetirizine and diphenhydramine as premedication for OCR infusions.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This 6-month randomized controlled pilot study will determine whether there is some evidence that cetirizine is better tolerated than diphenhydramine without an increase in IRRs. Fifty-two patients, 26 patients per arm, will be randomized in a 1:1 ratio to receive cetirizine or diphenhydramine as premedication prior to OCR infusions on day 0 (1st half dose of 300mg), day 14 (2nd half dose of 300mg) and week 24 (1st full dose of 600mg). Neurological exams and the estimated Expanded Disability Status Scale (EDSS) will be obtained at screening and week 24, as well as premature termination visits, if applicable. Stanford Sleepiness Scale (SSS), and the Visual Analog Scale – Fatigue (VAS-F) will be administered at screening, baseline, day 14, and week 24. Modified Fatigue Impact Scale (MFIS) and Multiple Sclerosis Impact Scale (MSIS-29) will be administered at screening and week 24. MSIS-29 and MFIS will also be administered at premature termination, if applicable. Treatment Satisfaction Questionnaire for Medication (TSQM) will be administered at baseline, day 14, and week 24. TSQM, SSS, and VAS-F will be administered within 2 hours after each OCR infusion, followed by a phone call on the next business day following each infusion to collect and assess infusion reactions or other AEs.

3.2 RATIONALE FOR STUDY DESIGN

Shortly after the approval of OCR, we followed the premedication protocol used in OPERA I and II which included 100mg of methylprednisolone, 1 gram of acetaminophen, and 50mg of IV diphenhydramine. However, many patients experienced extreme sedation which caused severe drowsiness and impaired their ability to function, drive, or work during and after the infusion, and even the following day. As a result, we have decreased the dose of diphenhydramine to 25mg administered either IV or orally which has resulted in less, but still marked, drowsiness. Newer antihistamines such as cetirizine may be better tolerated; however, there is no evidence that they will be as effective in minimizing infusion reactions.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

The proportion of patients having an infusion-related reaction, as defined by the Common Terminology Criteria (CTCAE), version 4[3] during or after the first-half dose of the first infusion on day 0. Infusion-related reactions will be documented at the infusion clinic on the day of the infusion and reported by the patient at the follow-up phone call the next business day after the infusion.

3.3.2 Secondary Outcome Measures

The proportion of patients having an infusion-related reaction during or after receiving the second half dose infusion on day 14.

The proportion of patients having an infusion-related reaction during or after receiving the first full 600mg dose infusion on week 24.

TSQM (Treatment Satisfaction Questionnaire for Medication) score after the infusions on day 0, day 14, and week 24.

SSS (Stanford Sleepiness Scale) score after the infusions on day 0, day 14, and week 24.

VAS-F (Visual Analog Scale for Fatigue) score after the infusions on day 0, day 14, and week 24.

MFIS (Modified Fatigue Impact Scale) score at week 24.

Physical and psychological MSIS-29 (Multiple Sclerosis Impact Scale) scores at week 24.

3.4 SAFETY PLAN

Patients will be evaluated by a clinician at the start of the study and at week 24 prior to the 600mg OCR infusion. Phone visits will be conducted after each infusion (see Section 4.5, Study Assessments, and Appendix A, Study Flowchart).

A full neurological examination will be conducted at screening and week 24. 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 12/2020[4] is to pre-medicate with 100mg of methylprednisolone (or an equivalent corticosteroid) administered 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[4]].

For this study, all patients will receive 1,000mg of acetaminophen orally and 100mg of methylprednisolone via IV 30-60 minutes prior to each infusion. Additionally, patients will be randomized to receive either diphenhydramine 25mg orally or cetirizine 10mg orally 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

<u>Suggested Management of IRRs</u>

All CD20+ depleting agents administered via the intravenous route, including OCR, have been associated with acute IRRs. Symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia.

Patients should be observed for at least one hour after the completion of the infusion for any symptom of IRR. They will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

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 5.1, 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, applicable national and local health authorities, and IRB requirements. Any amendment to the study protocol must be approved by Providence IRB before implementation. AEs and protocol deviations must be reported according to the guideline of the IRB.

4.0 MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Patient selection will be based on meeting all of the required inclusion and exclusion criteria to be eligible to participate in the trial.

4.1.2 Inclusion Criteria

1. Male or female patient with relapsing or progressive forms of MS, age 18 to 70 inclusive at the time of consent.

2. Able to understand the purpose, responsibilities and risks of the study and provide signed informed consent.

3. Naïve to OCR and will receive OCR as part of standard of care for MS treatment.

4. No evidence, in the opinion of the investigators of significant cognitive limitation or psychiatric disorder that would interfere with the conduct of the study.

5. Estimated EDSS of ≤ 6.5 at screening.

6. Female patients of childbearing potential must practice effective contraception and continue contraception during the study.

4.1.3 Exclusion Criteria

1. Any mental condition of such that patient is unable to understand the nature, scope, and possible consequences of the study.

2. Evidence of active hepatitis B infection at screening.

3. Patients with untreated hepatitis C, or tuberculosis. Patients who have history of PML or known to be HIV positive, per standard care.

4. Any persistent or severe infection.

5. Pregnancy or lactation.

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

7. Current use of immunosuppressive medication, lymphocyte-depleting agents, or lymphocyte-trafficking blockers.

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

9. Any known allergy or inability to tolerate diphenhydramine or cetirizine.

4.2 METHOD OF TREATMENT ASSIGNMENT

Randomization will be based on a computer-generated sequence using a permuted block design with block size equal to four. Participants will be allocated in a 1:1 ratio of oral diphenhydramine to oral cetirizine. All patients on this study will receive OCR as part of their standard care.

4.3. STUDY TREATMENT

Patients will be enrolled and randomized to either the diphenhydramine or the cetirizine arm to be administered before their OCR doses, after informed consent and screening assessment have been completed. The premedication and OCR will be paid for by the patient or by the patient's insurance. Patients may receive any generic products of cetirizine or diphenhydramine that are available at their infusion center and do not require the same brand of the premedication for their subsequent infusions. The same brand does not need to be used at each OCR infusion, per patient.

4.3.1 Packaging, Preparation, Storage, Handling, Dosage, and Administration

Packaging, Preparation, Storage and Handling

The study team is not responsible for collecting or reviewing data on how the premedications or OCR were packaged, prepared, stored, or handled for the purposes of this trial.

The treating physician will refer to the specific prescribing information provided by the drug manufactures for detailed instructions on packaging, preparation, storage, and handling for both the premedications and OCR[4]. The standard of care process is to be followed.

Dosage and Administration

1. Patients will be randomized to either diphenhydramine 25mg orally or cetirizine 10mg orally. The patients randomized to diphenhydramine will receive diphenhydramine 25mg orally 30-60 minutes prior to each OCR infusion. The patients randomized to cetirizine will receive cetirizine 10mg orally 30-60 minutes prior to each OCR infusion.

   The treating physician will refer to the specific prescribing information provided by the drug manufactures for detailed instructions on administration of the premedications. The standard of care process is to be followed.

2. 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 at 24 weeks.

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

   The treating physician will refer to the OCR prescribing information for detailed instructions on administration[4]. The standard of care process is to be followed.

4.3.2 Dosage Modification

Dose modifications of diphenhydramine or cetirizine are not permitted. See section 3.4 for dose modifications of OCR in the case of IRRs.

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

Informed consent must be obtained before proceeding with the study assessments. See section 6.2 for the detailed description of the informed consent process.

4.5.1 Assessments during Treatment

Visit 1 or Screening Visit (-28 to -1 days prior to Baseline)

- Informed consent
- Eligibility review
- Demographic information
- Review of disease and medical history
- Review of prior and concomitant medications, including lifetime MS disease modifying therapy history
- Reason(s) for switching to OCR
- Vital signs (blood pressure, heart rate, oral temperature, weight, and height)
- Neurological exam (may be historical exam if completed within 28 days prior to consent)
- Confirmation of estimated EDSS of 0 to 6.5, inclusive
- Laboratory assessments:
  - Urine or serum pregnancy test (females of childbearing potential only)
  - CBC and LFTs (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)

    - Serum immunoglobulins, quantitative (may be historical laboratories if completed within 28 days prior to consent)
- SSS
- VAS-F
- MFIS
- MSIS-29
- Adverse events

Visit 2 or Baseline Visit (Day 0)

- Concomitant medications and adverse events
- Eligibility review (can be done day -7 to day 0)
- Randomization for premedication arm (can be done day -7 to day 0)
- Administration of premedication and OCR (300mg)
- Infusion reaction assessment
- TSMQ (Administered within 2 hours after OCR infusion, may be completed via phone)
- SSS (Administered within 2 hours after OCR infusion, may be completed via phone)
- VAS-F (Administered within 2 hours after OCR infusion, may be completed via phone)
- Phone Call (next business day) to assess infusion reactions and any other AEs

Visit 3 (Day 14 +/- 2 days from baseline)

- Concomitant medications and adverse events
- Administration of premedication and OCR (300mg)
- Infusion reaction assessment
- TSMQ (Administered within 2 hours after OCR infusion, may be completed via phone)
- SSS (Administered within 2 hours after OCR infusion, may be completed via phone)
- VAS-F (Administered within 2 hours after OCR infusion, may be completed via phone)
- Phone Call (next business day) to assess infusion reactions and any other AEs

Visit 4 (24 weeks +/- 14 days from baseline)

- Vital signs (blood pressure, heart rate, oral temperature, and weight)
- Neurological exam (must be completed pre-OCR infusion)
- Estimated EDSS (must be completed pre-OCR infusion)
- Concomitant medications and adverse events (AE reporting period continues 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. Reassess AEs via phone call at 30 days +7 from time of last dose or study termination.)
- Laboratory assessments:
    - Urine pregnancy test (females of childbearing potential only, if positive, confirm by serum pregnancy test)
    - CBC and LFTs
    - Serum immunoglobulins, quantitative
- Administration of premedication and OCR (600mg)
- Infusion reaction assessment

- TSMQ (Administered within 2 hours after OCR infusion, may be completed via phone)
- SSS (Administered within 2 hours after OCR infusion, may be completed via phone)
- VAS-F (Administered within 2 hours after OCR infusion, may be completed via phone)
- MFIS
- MSIS-29
- Phone call (next business day) to assess infusion reactions and any other AEs

Premature Termination Visit

If OCR or the premedication 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 patient 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 (blood pressure, heart rate, oral temperature, and weight)
- Neurological exam
- Estimated EDSS
- MFIS
- MSIS-29
- Concomitant medications and adverse events (AE reporting period continues 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. Reassess AEs via phone call at 30 days +7 from time of last dose or study termination.)
- Laboratory assessments:
    - CBC and LFTs
    - Serum immunoglobulins, quantitative
- Primary reason for discontinuation

Lost to Follow-up

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

1. Diphenhydramine or cetirizine must be discontinued for any of the following reasons:
    - Life-threatening or serious hypersensitivity reaction
    - Patient discontinues OCR therapy
    - Patient election to discontinue therapy (for any reason)

2. 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
- Multiple serious infections
- Patient election to discontinue therapy (for any reason)

4.7 PATIENT DISCONTINUATION

Patients may 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, Inc. and the Principal Investigator have 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

For the primary, non-inferiority endpoint, analysis will be on both the intention-to-treat and per-protocol populations (two-sample proportion non-inferiority test). Analysis for secondary endpoints will be on the intention-to-treat population. The intention-to-treat population is defined as all randomized patients, and the per-protocol population will be those who completed the study as per protocol specification.

If the study is terminated before planned enrollment is reached, only descriptive analysis will be performed.

4.9.2 Analysis of Treatment Group Comparability

Baseline characteristics will be reported by arm. Categorical variables will be summarized as frequency and proportion and continuous variables by mean and standard deviation or median and 25^{th} and 75^{th} percentiles, as appropriate based on normality.

4.9.3 Efficacy Analysis

a. Primary Endpoint

The proportion of patients with IRRs during or after the first infusion on day 0 will be reported for each arm. Cetirizine will be considered non-inferior to diphenhydramine if the lower limit of the two-sided, 90% confidence interval for the difference in proportions (diphenhydramine-cetirizine) is greater than the non-inferiority margin of -0.30[5].

b. Secondary Endpoints

The proportion of patients with IRRs during or after infusion will be compared using Fisher's exact tests at day 14 and week 24, as we expect the proportion of IRRs to be small at these time points based on OPERA I and II. Additionally, the proportion of IRRs after each infusion will be plotted overall and by severity for the two arms. At day 0, day 14, and week 24, TSQM scores will be compared between arms using Wilcoxon Rank Sum or two-sample t-tests, as appropriate based on normality, and SSS and VAS-F scores will be compared using Wilcoxon rank sum tests. MFIS, physical MSIS-29, and psychological MSIS-29 will be compared at week 24 using multiple linear regression with analysis of covariance (ANCOVA), adjusting for the screening score.

4.9.4 Safety Analysis

Information on the timing, severity, relationship to premedication, relationship to OCR 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

Baseline characteristics and outcomes for patients who followed protocol and completed the study, violated protocol, and discontinued the study will be reported separately. The reasons for discontinuing or violating protocol will be reported and any influence on the trial results will be discussed. Any other irregularities that result in missing data will be fully identified and discussed.

For the primary endpoint using the intention-to-treat population, the missing data mechanism will be examined and multiple imputation or best/worst imputation will be used, assuming missing at random. For the primary endpoint, assessed at day 0, we expect missing data will be limited.

4.9.6 Determination of Sample Size

Based on the results of the OPERA I and II trials, we assume that 25% of patients in the diphenhydramine arm and 25% of patients in the cetirizine arm will experience mild to severe IRRs during or after receiving the first infusion on day 0. Assuming that a 30% absolute difference (i.e. margin = - 0.30) in the proportion of patients with IRRs between premedication groups is the maximum relevant difference when holding that cetirizine is not inferior to diphenhydramine, 26 patients per arm are needed to achieve 80% power with a one-sided significance level of 0.05. As this is a pilot study, we allow a large margin to establish some evidence of non-inferiority. The two-sample proportion test for non-inferiority in the R package Trial Size was used for the calculation.

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

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 premedication and OCR. 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. MS related symptoms are not to be reported as AEs unless, in the opinion of the investigator, the symptoms are unusually serious and relevant. Any AE of severity moderate or higher, requires follow up until resolution or stabilization by the treating investigator beyond the final study contact as part of standard care.

All AEs should be recorded in the patient's AE case report form regardless of severity or relationship to the premedication or OCR.

Infusion-Related Reactions (IRRs)

Adverse events that occur during or within 24 hours after OCR administration and are judged to be related to OCR infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of OCR, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

Investigators should consider a local IRR for any symptoms affecting the skin and localized to only one place. Any other IRR should be considered systemic.

Severity

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.

Relationship to Premedication and OCR

The relationship or association of the AE to the premedication and OCR will be characterized as follows:

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

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

Possibly — Any reaction that follows a reasonable temporal sequence from administration of 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 patient's clinical state or other modes of therapy administered to the patient.

Related — Any reaction that follows a reasonable temporal sequence from administration of 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 the premedication or 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 the premedication, OCR, or other protocol-imposed intervention, whether or not there is a causal relationship with OCR or the premedication.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period.

- Complications that occur as a result of protocol-mandated interventions (e.g., procedures such as OCR infusions).

- If applicable, AEs that occur after signing consent, 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 patient 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 patient'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 premedication and/or OCR.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient 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 AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA (as applicable), appropriate IRB(s) (as applicable), 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 patient, 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 OCR (see above guidance) and premedication, and actions taken.

Expected versus unexpected is to be evaluated for SAEs.

Expected adverse events are those adverse events that are listed or characterized in the current prescribing information[4].

Unexpected adverse events are those not listed in the prescribing information[4] 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.

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

5.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient 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 pre-existing 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 patient 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 patient 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. Pregnancy

Female patients will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of OCR. If a pregnancy occurs during this time period for a female patient, a report should be completed and submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur, 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 patient exposed to the premedications and/or OCR should be reported as an SAE.

Additional information on any ocrelizumab-exposed pregnancy and infant will be requested by Genentech/Roche 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).

Pregnancies will not be reported to the premedication manufacture.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior OCR exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

SAEs will not be reported to the premedication manufacture after the end of the patient's study participation.

g. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission Verification to ensure that all single case reports have been adequately received by Genentech, Inc. via Providence Brain and Spine Institute emailing Genentech, Inc. a quarterly line-listing documenting single case reports sent by Providence Brain and Spine Institute to Genentech, Inc. 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, Inc. 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, Inc. shall be forwarded by Providence Brain and Spine Institute to Genentech, Inc. within five (5) calendar days from request by Genentech, Inc.

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

Case Transmission Verification will not be completed for the premedication manufactures.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of OCR. AESIs are not being reported for the premedications.

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 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:

  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.

i. Exchange of Single Case Reports

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

Investigators must report all of the above mentioned single case reports adequately to Genentech, Inc., Providence Health & Services, and the premedication manufactures (if applicable) within the timelines described below. The completed applicable report form should be submitted immediately upon completion to:

Genentech, Inc. Drug Safety:
Email: usds_aereporting-d@gene.com
OR
Fax: (650) 238-6067

Providence Health & Services Regional Research Regulatory Office:
Email: Regulatory Associate noted on Sponsor Contact List and CC
tiffany.gervasi-follmar@providence.org (Study Manager)
OR
Fax: (503) 215-6547 (Regulatory) and (503) 216-1039 (Study Manager)

Cetirizine manufacturer:
Follow manufacture guidance to report drug safety information.

Diphenhydramine manufacturer:
Follow manufacture guidance to report drug safety information.

Genentech, Inc. Investigational Medicinal Product Complaints (without an AE):
Communicate details on form verbally to the Product Complaint Hotline, document communication in subject source.

Phone: (800) 334-0290 (M-F, 5am to 5pm PST)

Relevant follow-up information should be submitted to each applicable party as soon as it becomes available for each type of report, if applicable [SAEs, AESIs, and Other Special Situations (including pregnancy)].

- **Serious Adverse Drug Reactions (SADRs)**
  Serious AE reports that are related to OCR shall be transmitted to Genentech, Inc. Drug Safety within fifteen (15) calendar days of the awareness date.

  Serious AE reports that are related to the premedication shall be transmitted to the manufacture within fifteen (15) calendar days of the awareness date.

  All SADR reports should be transmitted to the Providence Health & Services Regional Research Office within 24 hours of knowledge of the event.

  Use the MedWatch 3500A form for reporting all SASRs. Include the Safety Reporting Cover Sheet (Appendix B) for all transmissions.

- **Other SAEs**
  Serious AE reports that are unrelated to OCR shall be transmitted to Genentech, Inc. Drug Safety within thirty (30) calendar days of the awareness date.

  Serious AE reports that are unrelated to the premedication will not be reported to the premedication manufacture.

  All other SAE reports should be transmitted to the Providence Health & Services Regional Research Office within 24 hours of knowledge of the event.

  Use the MedWatch 3500A form for reporting all other SAEs. Include the Safety Reporting Cover Sheet (Appendix B) for all transmissions.

- **AESIs**
  AESIs shall be transmitted to Genentech, Inc. Drug Safety within fifteen (15) calendar days of the awareness date.

  All AESI reports should be transmitted to the Providence Health & Services Regional Research Office within fifteen (15) calendar days of the awareness date.

  Use the MedWatch 3500A form for reporting all AESIs. Include the Safety Reporting Cover Sheet (Appendix B) for all transmissions.

  AESIs will not be reported to the premedication manufactures.

- **Special Situation Reports**
  Pregnancy Reports
  Pregnancy in a female patient shall be transmitted to Genentech, Inc. Drug Safety within thirty (30) calendar days of the awareness date.

All pregnancy reports should be transmitted to the Providence Health & Services Regional Research Office within thirty (30) calendar days of the awareness date.

Use the Clinical Trial Pregnancy Reporting (Appendix C) for reporting all pregnancies.

Pregnancies will not be reported to the premedication manufacture.

- **Other Special Situation Reports**

  In addition to SAEs, AESIs, and pregnancy reports, the following Other Special Situations Reports should be collected and transmitted to Genentech, Inc. Drug Safety, even in the absence of an AE, within thirty (30) calendar days:

  - Data related to OCR usage during pregnancy or breastfeeding
  - Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure of OCR, with or without association with an AE/SAE unless otherwise specified in the protocol
  - Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)

  All Other Special Situation Reports should be transmitted to the Providence Health & Services Regional Research Office within thirty (30) calendar days of the awareness date.

  Use the MedWatch 3500A form for reporting all Other Special Situation Reports. Include the Safety Reporting Cover Sheet (Appendix B) for all transmissions.

  Other Special Situation Reports are not being transmitted to the premedication manufactures.

In addition, reasonable attempts should 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**

  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.

  All OCR Product Complaints with an AE should be transmitted to Genentech, Inc. Drug Safety within fifteen (15) calendar days of the awareness date.

  All OCR Product Complaints without an AE should be transmitted to Genentech, Inc. Investigational Medicinal Product Complaints within fifteen (15) calendar days of the awareness date.

All OCR Product Complaints with or without an AE should be transmitted to the Providence Health & Services Regional Research Office within thirty (15) calendar days of the awareness date.

Use the MedWatch 3500A form for reporting all OCR Product Complaints. Include the Safety Reporting Cover Sheet (Appendix B) for all transmissions.

Product Complaints are not being transmitted to the premedication manufactures.

j. Aggregate Reports

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

Providence Brain and Spine Institute will forward a copy of the manuscript to Genentech, Inc. before the manuscript is submitted for publication.

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 description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Investigator's assessment of the relationship of the adverse event to the premedication and OCR
- Expected versus unexpected event

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 submitting it with a cover letter including patient identifiers (i.e. D.O.B. initials, 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)

Occasionally, Genentech, Inc., Providence Health & Services, or the premedication manufactures may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

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

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech, Inc. 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.

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

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 the following parties:

Genentech, Inc. Drug Safety:
Phone: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Providence Health & Services:
Phone: Regulatory Associate noted on Sponsor Contact List or (503) 216-1023 (Study Manager)
Email: Regulatory Associate noted on Sponsor Contact List or tiffany.gervasi-follmar@providence.org (Study Manager)

Cetirizine manufacturer:
Follow the manufacture's guidelines for drug safety reporting questions.

Diphenhydramine manufacturer:
Follow the manufacture's guidelines for drug safety reporting questions.

5.5 STUDY CLOSE-OUT

Any literature articles that are a result of the study should be sent to Genentech, Inc./Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:
Email: Ocrelizumab-iis-d@gene.com

And to Genentech Inc. Drug Safety CTV oversight mail box at:
Email: 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 Inc./Roche shall have the final say and control over safety queries relating to OCR. Providence Brain and Spine Institute 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 Inc./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 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 the Sponsor of the Study will be primarily responsible for assessment of the benefit-risk balance of the Study.

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

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

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

5.8 COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT/ AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE 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 AE 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.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Genentech Inc. or a Genentech Inc. 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 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 case history for each patient shall document that informed consent was obtained prior to participation in the study. The IRB approved informed consent will be signed by the patient before any screening assessments or procedures are performed. A copy of the informed consent document must be provided to the patient. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each patient'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 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 (premedications) 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, Inc. (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 the 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 according to the monitoring plan. 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

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

Upon the patient'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 Inc., 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	Visit 1 Screening (day -28 to -1)	Visit 2 Baseline (day 0)	Visit 3 (day 14±2 days)	Visit 4 (week 24±14 days)	Premature Termination Visit
Informed consent	X				
Eligibility review (INC/EXC)	X	X[I]			
Randomization		X[I]			
Demographics	X				
Vitals[D]	X			X	X
Disease & medical history	X				
Reason(s) for switching to OCR	X				
Neurological exam	X[E]			X[K]	X
EDSS (estimated)	X			X[K]	X
CBC & LFTs	X[E]			X	X
Serum immunoglobulins, quantitative	X[E]			X	X
Urine or serum pregnancy test[F]	X			X	
Hepatitis B testing	X[G]				
Premedication		X	X	X	
OCR infusion[H]		X	X	X	
Infusion reaction assessment		X	X	X	
Phone call		X[B]	X[B]	X[B, J]	X[J]
TSMQ		X[A]	X[A]	X[A]	
MFIS & MSIS-29	X			X	X
VAS-F	X	X[A]	X[A]	X[A]	
SSS	X	X[A]	X[A]	X[A]	
AEs	X	X	X	X	X
Con meds	X[C]	X	X	X	X
Primary reason for discontinuation					X

A: Administered within 2 hours post OCR infusion, may be completed via phone.
B: On next business day after OCR infusion to assess infusion reactions and any other AEs.
C: Prior & concomitant medications, including lifetime MS disease modifying therapy history.
D: To include heart rate, blood pressure, oral temperature, and weight. At screening only, also collect height.
E: May be historical if completed within 28 days prior to consent.
F: Females of childbearing potential only. Urine or serum test at screening. Urine test at week 24. If positive urine test, confirm by serum pregnancy test.
G: May be historical if completed within 6 months prior to consent.
H: 300mg IV at Visits 2 and 3, 600mg IV at Visit 4.
I: Can be done day -7 to day 0.
J: AE reporting period continues 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. Reassess AEs via phone call at 30 days +7 from time of last dose or study termination.
K: Must be completed pre-OCR infusion.

APPENDIX B: SAFETY REPORTING COVER SHEET

Genentech
A Member of the Roche Group

SAFETY REPORTING 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)

Patient 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

APPENDIX C: CLINICAL TRIAL PREGNANCY REPORTING FORM

CLINICAL TRIAL PREGNANCY REPORTING FORM

Instructions:

Complete all Essential Elements (fields marked with ♦ and ♦). All fields marked with ♦* are minimal data elements and, if missing, the Pregnancy form will be considered invalid.*

- *This form is to be used to report pregnancy information and any events associated with the fetus/baby*
- *Complete in English, writing clearly in block capitals using black ink, or complete the form electronically and print*
- *For dates spell out the first three letters of the month, dd/MMM/yyyy e.g., 07 Apr 2010*
- *For multiple births complete one form per infant*
- *All sections of this form (other than the AER Number and Company Received Date) must be completed by the Investigator/Designee*
- *Follow up information can be provided at any time until the outcome of the pregnancy is known*

♦ Protocol No:	Site No:	♦* Screening No:	♦ Subject No (Randomization or Enrolment or CRF No):

For Internal Use Only	AER No:		Company Received Date	

1. SERIOUS ADVERSE EVENTS PREVIOUSLY REPORTED FOR CLINICAL TRIAL SUBJECT		
☐ Yes ☐ No	♦* Study Drug Name:	
If yes, Provide:	Event(s):	

2. PERSONAL DATA for Clinical Trial Subject *Consider local laws regarding data privacy when completing this section*					
♦*Birth Date	*dd/MMM/yyyy*		♦*Sex	☐ Male ☐ Female	
Height (Select unit):		☐ cm ☐ inch	Weight (Select unit):		☐ kg ☐ lb
Race:	☐ Caucasian	☐ Black	☐ Asian	☐ Other Specify:	
If Clinical Trial Subject is male, has the female partner consented to pregnancy follow up?					☐ Yes ☐ No
♦*Personal Data for Female Partner: *(Only complete this section for a pregnancy of a partner of a male subject)* *Consider local laws regarding data privacy when completing this section.*					
♦*Birth Date	*dd/MMM/yyyy*				
Height (Select unit):		☐ cm ☐ inch	Weight (Select unit):		☐ kg ☐ lb
Race:	☐ Caucasian	☐ Black	☐ Asian	☐ Other Specify:	

3. PREGNANCY INFORMATION *for Clinical Trial Subject or Female Partner*			
Last menstrual period Date *(dd/MMM/yyyy):*		☐ estimated*	**check if the documented date is estimated*
Conception Date *(dd/MMM/yyyy):*		☐ estimated*	
Estimated Delivery Date *(dd/MMM/yyyy):*			

♦* **Pregnancy Outcome** *Mark current status of pregnancy including date where appropriate*		
Pregnancy ongoing ☐	Unknown ☐	Lost to follow up ☐
Therapeutic Abortion ☐	Spontaneous/Missed Abortion ☐	Ectopic Pregnancy ☐
Live Birth ☐	Elective Birth ☐	Still Birth ☐ (complete date of death in section 4)
Date of Abortion/Live Birth *(dd/MMM/yyyy):*		

4. ♦* BIRTH OUTCOME *Check to indicate the current status of the fetus/baby. Where applicable specify the details*			
Unknown ☐ *(go to section 6)*	Not reported ☐ *(go to section 6)*	Normal ☐ If yes: ☐ Vaginal delivery ☐ C-Section *(go to section 5)*	Abnormal ☐ If yes: ☐ Vaginal delivery ☐ C-Section *(Birth defects/congenital abnormalities and other events experienced by the fetus/baby)*
Specify abnormality:			Death ☐ (*e.g., intrauterine death, still birth, post-delivery death)*
Specify cause of Death:			Date of Death *(dd/MMM/yyyy):*

♦ **Event Seriousness**		
Was the event (i.e., birth outcome) serious?	☐ Yes ☐ No *If Yes, check all that apply:*	
	☐ Results in death	☐ Requires prolongation of existing hospitalization
	☐ Life-threatening	☐ Persistent or significant disability / incapacity
	☐ Requires in-patient hospitalization	☐ Congenital anomaly / birth defect
OR *only when no other criteria applies*	☐ Medically Significant	

♦ **Possible Causes of the Event** *(i.e., birth outcome)*	
☐ Study Treatment *(Includes the Investigational Product, Comparator or Placebo i.e., excipients)*	☐ Yes ☐ No
Specify study drug(s):	
This option indicates that there is a reasonable possibility of a causal relationship between the study drug(s) and the event	

Other suspect causes *(select all that apply):*		
☐ None (only applicable if study treatment is related)		
☐ Disease under study	Specify:	
☐ Medical history or concurrent illness	Specify:	
☐ Concomitant medication	Specify:	
☐ Protocol related procedure	Specify:	
☐ Other *(e.g., accident, erroneous administration, intercurrent/unrelated illness):*	Specify:	

5. INFANT INFORMATION					
Gestational week at birth:		If multiple birth (e.g., twins) indicate number:		Sex:	☐ Male ☐ Female ☐ Unknown
Length:		☐ cm ☐ inch	Weight		☐ kg ☐ lb
Head Circumference:		☐ cm ☐ inch	Apgar Score (0-10) *(at 10 minutes)*		

6. RELEVANT DRUG INFORMATION OF CLINICAL TRIAL SUBJECT *Please complete drug section for all relevant medications taken before pregnancy by clinical trial subject including study*

drug. If study design is blinded enter Study Drug/Comparator in name field

Reported Drug Name *(generic or trade name)*	**Indication**	**Time of Exposure** *(Pre-conception, 1st, 2nd, 3rd trimester)*	**Route**	**Dosing Regimen and Frequency**	**Start Date** *(dd/MMM/yyyy)*	**End Date** *(dd/MMM/yyyy)*	**Ongoing**
							☐
							☐
							☐
							☐

7. **RELEVANT DRUG INFORMATION OF MOTHER** ***(Only complete this section for a pregnancy of a partner of a male subject)***

Please complete drug section for all relevant medications taken before and during pregnancy by the female partner if not the clinical trial subject

Reported Drug Name *(generic or trade name)*	**Indication**	**Time of Exposure** *(Pre-conception, 1st, 2nd, 3rd trimester)*	**Route**	**Dosing Regimen and Frequency**	**Start Date** *(dd/MMM/yyyy)*	**End Date** *(dd/MMM/yyyy)*	**Ongoing**
							☐
							☐
							☐
							☐
							☐

8. RELEVANT MEDICAL HISTORY OF MOTHER

Contraception *(If known enter the method used at time of conception; may choose more than one)*		**Number of Previous Pregnancies** *(Not including current pregnancy)*		**Risk Factors** *(Enter all known relevant risk factors)*
☐ Unknown	☐ Infertility (male)	☐ Unknown		☐ Unknown
☐ None	☐ Infertility (female)	☐ None		☐ Alcohol
☐ Rhythm	☐ Surgical Sterilization	Pregnancies:		☐ Diabetes
☐ Condom	☐ Contraceptive Medication	Abortions:		☐ Infection
☐ Diaphragm	☐ Withdrawal	Spontaneous / Missed abortions		☐ Smoking
☐ IUD	☐ Abstinence	Stillbirths:		☐ Drug abuse
☐ Spermicide		Deliveries		☐ None
		Child born with defects:		☐ Other Specify:

9. RELEVANT LAB TESTS AND PROCEDURES CARRIED OUT ON MOTHER

Enter what tests were performed, e.g., ultrasound, amniocentesis; name and results of each one, plus units and normal ranges if applicable. If you need more space, continue in section 10

Lab Test/ Procedure	**Date of Test** ***(dd/MMM/yyyy)***	**Result**

10. ADDITIONAL DETAILS OF PREGNANCY, FETUS AND/OR BABY *Enter any information which could not be entered in the other sections of the form. Please identify the section to which the information applies.*

REFERENCES

1. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *The New England journal of medicine.* Jan 19 2017;376(3):221-234.

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3. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed 02/13/19, 2019.

4. Genentech Inc. Ocrevus: Highlights of Prescribing Information. 2020; https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed 03/18/2021.

5. US Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. 2016.