PROTOCOL

STUDY TITLE: Pilot study of meningeal inflammation on 7T MRI as a tool for measuring and predicting ocrelizumab response in multiple sclerosis

STUDY DRUG: none

SUPPORT PROVIDED BY: Genentech, Inc.

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STUDY NUMBER: RO-IIS-2017-10146

PROTOCOL VERSION/DATE: Version 1.0, 10/12/2017

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1. INTRODUCTION

Meningeal inflammation is an increasingly recognized pathological phenomenon in multiple sclerosis.[1] Autopsy data demonstrates some element of meningeal inflammation in nearly 90% of patients with MS,[1, 2] and 40-50% of patients with MS have tertiary lymphoid structures (in the form of lymphoid follicles) in the meninges.[3, 4] These follicles contain a number of cells in the B-cell lineage, including plasma cells, plasmablasts, and memory B-cells. Autopsy data suggests that the inflammatory effects of meningeal inflammation may result in direct cortical injury, as a gradient of cortical neuronal loss and demyelination is found emanating outwards from regions of organized meningeal inflammation.[4, 5]

In order to confirm or refute the importance of meningeal inflammation in MS and its relationship to the development of cortical damage, it is necessary to utilize an *in vivo* marker of meningeal inflammation. Some have suggested post-contrast 3D-FLAIR MRI as such a marker, given sensitivity of post-contrast 3D-FLAIR to other meningeal diseases.[6] A schematic showing the potential mechanism by which cortical gray matter lesions and gadolinium contrast leakage could both be caused by meningeal inflammation is shown in Figure 1.

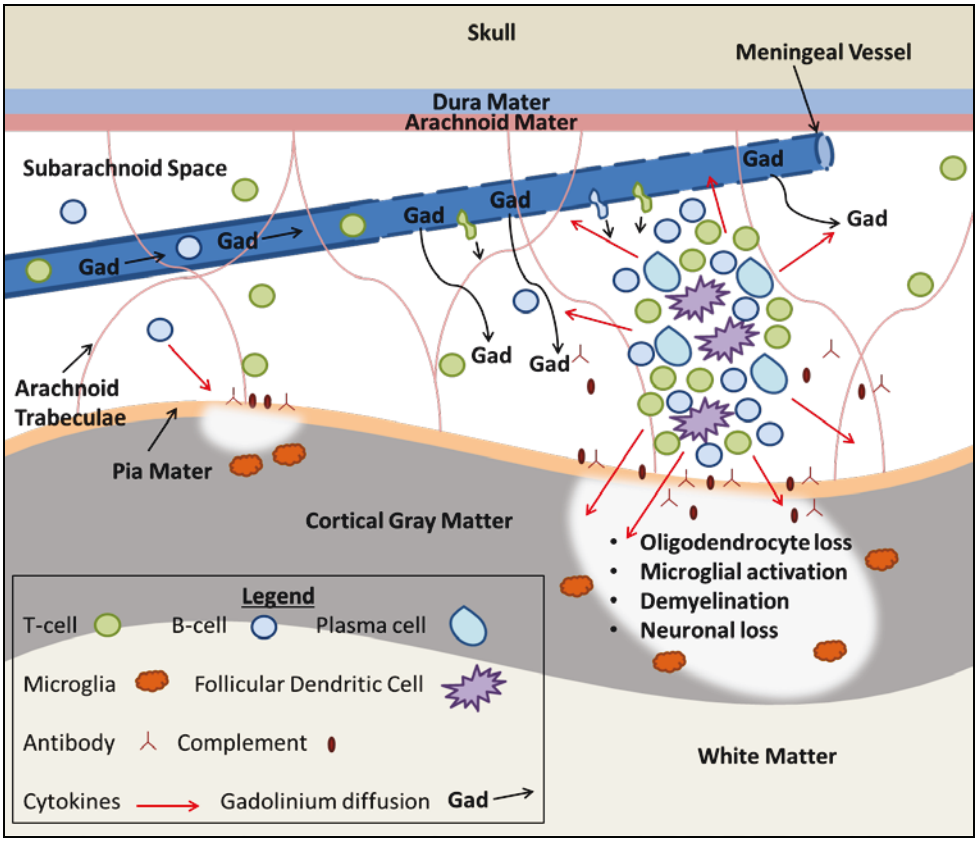

Figure 1: Proposed mechanism for cortical pathology and leptomeningeal gadolinium enhancement due to meningeal inflammation in multiple sclerosis. Clusters of autoreactive inflammatory cells in the subarachnoid space, sometimes organized into tertiary lymphoid follicles, release inflammatory cytokines that trigger opening of the blood/CSF barrier on adjacent meningeal vessels. Recruitment of circulatory inflammatory cells results, and, by proxy, intravenous gadolinium may leak into the subarachnoid space. Arachnoid trabeculae and inflammatory fibrosis may permit local pooling of gadolinium, especially in deep sulci. Inflammatory cytokines also recruit and activate cortical microglia, which, along with cellular inflammation and antibody and complement deposition, leads to local cortical injury.

Initial results published by Absinta et al[7] using the post-contrast 3D-FLAIR technique on a 3 Tesla (3T) MRI scanner were promising. However, only approximately 25% of

participants in this study with MS were found to have leptomeningeal enhancement- far less than what is found at autopsy.

Although a more recent publication utilizing a 3D-FLAIR technique at 3T modified for enhanced lesion contrast showed enhancement in the leptomeningeal space in 50% of MS participants,[8] both of these studies mainly used post-contrast FLAIR scans and did not co-register these scans to a pre-contrast image for comparison. Given this, it is quite possible that many of the 'enhancing' regions described may have been present on pre-contrast images, making the frequency of true leptomeningeal enhancement at 3T less than reported in these publications. In fact, this same research group recently presented data showing that removal of false positives with a pre-contrast FLAIR image reduces the rate of enhancement in the meninges by their technique to ~28% (Zivadinov et al., presented at the Annual AAN Meeting, Boston, MA).

Our own recently published data[9] suggests that post-contrast magnetization prepared FLAIR (MPFLAIR) MRI on at 7T MRI scanner shows leptomeningeal enhancement that is MS-specific in 76% of participants. This data was acquired using a high resolution ($0.7mm^3$) whole-brain sequence, acquired before contrast, and again 20 minutes after contrast administration. Post-contrast images were co-registered to the pre-contrast image and a digital subtraction image was created to only highlight true areas of contrast enhancement (example in Figure 2). We identified amorphous contrast leakage into the subarachnoid space (Figure 3), typically located in deep sulci, regions typical for meningeal inflammation at autopsy. Clearly and concisely state the objectives and which questions are to be addressed by the study.

We also have demonstrated that findings of leptomeningeal enhancement at 7T in MS are a stable finding, with 86% of foci found on a baseline scan to be present on a follow up 1 year later (Jonas et al., to be presented at the 2017 Meeting of the Radiological Society of North America, Chicago, IL). The longitudinal stability of this finding indicates its potential as a biomarker that can be tracked over time, possibly for treatment effect.

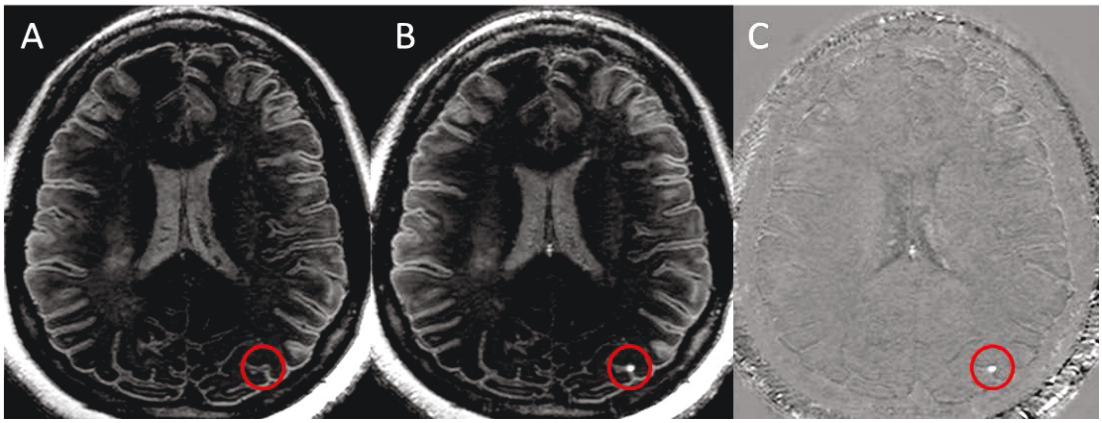

Figure 2: Method for identifying enhancing foci. Shown are co-registered pre-contrast MPFLAIR (A) and post-contrast MPFLAIR (B) and a digital subtraction image (C). The location of a hyperintensity noted on subtraction is highlighted in red on all 3 images.

We suggest that our 7T technique is a more accurate marker of meningeal inflammation in MS given the much higher frequency of enhancement seen at 7T compared to 3T and the accuracy of using a post minus pre-contrast subtraction image. Our own work and the work of others have also demonstrated the superiority of 7T MRI for the identification of cortical pathology in MS.

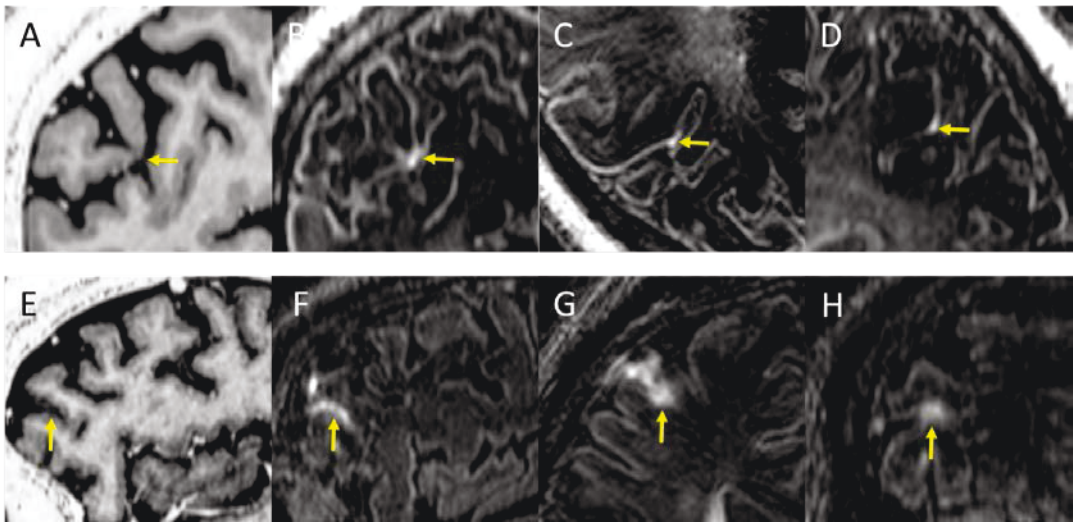

Figure 3: Examples of enhancing leptomeningeal foci. Shown are portions of a sagittal MP2RAGE (A,E) and corresponding slice on MPFLAIR (B,F), with yellow arrow indicating the location of an enhancing focus on MPFLAIR. Foci are shown also in axial (C, G) and coronal (D,H) planes to demonstrate amorphous spreading of contrast in the subarachnoid space.

Given the mechanism of action of ocrelizumab (anti-CD20),[10, 11] and the potential that such therapies may impact meningeal inflammation in MS, we wish to address whether or not 7T MRI techniques for visualization of meningeal inflammation and cortical pathology may act as a biomarker of treatment response.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

In this study, we will aim to accumulate initial, pilot data as to the following hypotheses:

- Use of ocrelizumab will reduce the extent of leptomeningeal enhancement seen in patients with MS.
- A reduction in the extent of leptomeningeal enhancing foci will correlate with clinical response in patients receiving ocrelizumab for MS.
- A reduction in the extent of leptomeningeal enhancing foci will correlate with the prevention of the development of new cortical lesions in those receiving ocrelizumab for MS.

2.2 SECONDARY OBJECTIVES

None

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Twenty-two (22) participants will be recruited from the University of Maryland Center for Multiple Sclerosis Treatment and Research. Participants will be included if they are aged 18-65, have a diagnosis of relapsing or progressive multiple sclerosis per revised 2010 McDonald Criteria, and are planning to begin ocrelizumab therapy for multiple sclerosis. This will include patients enrolling in clinical trials of ocrelizumab and patients being started on commercial drug (after FDA approval). Participants will be excluded if

they are unable to undergo an MRI due to metallic implants/devices or claustrophobia, have a history of allergy to gadolinium contrast, or are unable to provide informed consent.

All participants will undergo a baseline/screening study visit prior to initiation of ocrelizumab. This will include signing of informed consent, a clinical interview to collect demographic and clinical data, a physical examination to calculate the EDSS score, and implementation of the component tests of the Multiple Sclerosis Functional Composite (MSFC). All participants will then undergo an MRI on a 7T Philips Achieva scanner (housed at the Kennedy Krieger Institute, Baltimore, MD). This will be a whole brain MRI, including 0.7mm^3 resolution magnetization prepared 2 rapid acquisition gradient echo (MP2RAGE) and MPFLAIR images acquired both pre- and post-intravenous infusion of gadolinium contrast.

MP2RAGE images will be processed to create T1 maps and T1-weighted images. All images (MPFLAIR included) will be co-registered to the pre-contrast MP2RAGE T1 map. Subtraction images will be created by subtracting the pre-contrast MPFLAIR scan from post-contrast images. Regions of hyperintensity on the subtraction image will be reviewed on anatomical images, and marked as regions of leptomeningeal enhancement if they have an amorphous appearance and are present in the leptomeningeal space.

Participants who are found to have leptomeningeal enhancement on their baseline scan will be considered as having passed screening and will proceed with further study procedures. Those that do not have meningeal enhancement on a baseline scan will not return for a follow up visit.

Participants who have passed screening (and thus have meningeal enhancement on their baseline scan) will then undergo initiation of ocrelizumab per clinical trial or commercial drug protocol as previously planned by their treating neurologists. Participants will then return for a follow up visit within 1 month after their 12 month ocrelizumab infusion. All of the above study procedures will be repeated on that date.

Follow up images for each subject will undergo co-registration to the pre-contrast MP2RAGE T1 map. This will allow co-registered review of baseline and 1 year follow up MPFLAIR images side-by-side for review of the presence or absence of enhancing foci noted at baseline on the 1 year follow up scan. Subtraction images will also be created utilizing the 1 year pre- and post-contrast MPFLAIR scan for quantification of the number of enhancing foci on the 1 year follow up scan by the same procedures as above. A semi-automated region growing painting tool will be used to create masks over areas of contrast enhancement, which will be used to quantify enhancing focus volume on the baseline and follow up scan. Further, subtraction mapping will be utilized to highlight regions of hypointensity present in the cortex on MP2RAGE T1 that were not present on baseline MP2RAGE T1, which would indicate a new cortical lesion at follow up.

3.2 RATIONALE FOR STUDY DESIGN

This study is a non-interventional, observational clinical-imaging study. Participants in this study will be recruited after a decision has been made by their treating physician to place them on ocrelizumab for standard clinical purposes. Imaging and clinical observations will be then taken before and after initiation of the medication, and we will observe if the use of ocrelizumab has any impact on the proposed imaging measures and if the imaging measures are linked with treatment response. This study design was

chosen given the pilot nature of the proposal and the existence of FDA approval for the drug (thus negating the need to propose an interventional clinical trial).

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measure

Primary Endpoint: Reduction in the number of enhancing leptomeningeal foci on 1 year follow up compared to baseline in MS patients treated with ocrelizumab.

3.3.2 Secondary Outcome Measures

Secondary Endpoint: Reduction in the proportion of participants with meningeal enhancement after treatment with ocrelizumab compared to pre-treatment baseline.

Other:

- Reduction in the volume of contrast enhancement on follow up compared to baseline.

- Difference in the proportion of those with no clinical evidence of disease activity (no relapses or disability progression) in participants who experience a reduction in enhancing leptomeningeal foci after treatment with ocrelizumab versus those who do not.
- Difference in the proportion of those with no new cortical lesions on 1 year follow up scans in participants who experience a reduction in enhancing leptomeningeal foci after treatment with ocrelizumab versus those who do not.

3.3.3 Ancillary Safety Outcome Measures

None

3.4 SAFETY PLAN

This is a non-interventional, observational study, and thus ocrelizumab will not be directly prescribed or given as a study procedure (at the discretion of clinical treating physician. However, participants will be screened for ocrelizumab-related adverse events at the time of their study visits and any AEs or SAEs will be reported to Genentech as described in section 5 of the protocol.

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4.0 MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

4.1.2 Inclusion Criteria

- A diagnosis of relapsing or primary progressive multiple sclerosis according to revised 2010 McDonald Criteria
- Ages 18 to 65, inclusive
- Have been prescribed ocrelizumab by their treating physician for treatment of multiple sclerosis, with the 1st infusion to occur within 30 days of enrollment

4.1.3 Exclusion Criteria

- Inability to provide informed consent
- Inability to undergo MRI due to implantable devices or metallic foreign bodies considered unsafe in the MRI magnet
- Known severe allergic reaction (anaphylaxis) in the past to gadolinium contrast
- A current diagnosis of severe kidney failure and/or use of hemodialysis
- Currently pregnant or lactating
- History of a seizure disorder

4.1.4 Recruitment Plan

Information on patients being prescribed ocrelizumab for multiple sclerosis at the University of Maryland Center for Treatment and Research in MS will be reviewed to determine if participants may meet initial screening criteria. All such participants will be contacted to determine their interest in participation. During this process, attempts will be made to recruit a cohort equally distributed between patients with relapsing MS and primary progressive MS. However, if recruitment of progressive participants according to the recruitment timeline proves difficult, participants with relapsing MS will be recruited in lieu of such participants.

4.2 METHOD OF TREATMENT ASSIGNMENT

N/A

4.3. STUDY TREATMENT

N/A

4.3.1 Dosage, Preparation, Administration and Storage

N/A

4.3.2 Dosage Modification

N/A

4.3.3 Overdosage

N/A

4.4 CONCOMITANT AND EXCLUDED THERAPY

None

4.5 STUDY ASSESSMENTS

4.5.1 Baseline visit

- This visit should occur within 30 days prior to their first dose of ocrelizumab.
- Informed consent will be obtained prior to any study procedures
- A clinical interview will be conducted to collect demographic and clinical data for reporting on a case report form
- A neurological examination will be performed to obtain an EDSS score
- The timed 25 foot walk, 9-hole peg test, and PASAT will be performed to obtain an MSFC score
- Serum test for creatinine and BUN
- An MRI of the brain with/without gadolinium contrast will be obtained on a 7T scanner
- MRI images will be reviewed for the presence/absence of leptomeningeal enhancement on post-contrast MPFLAIR sequences. Participants without gadolinium enhancement will be excluded from further study. Only participants with gadolinium enhancement will return for the follow up assessment.

4.5.2 Follow-Up Assessment

This visit should occur approximately 1 year from the baseline/screening visit, and within 30 days after the participant's month 12 ocrelizumab infusion.

- An updated clinical interview will be conducted to collect demographic and clinical data for reporting on a case report form
- A neurological examination will be performed to obtain an EDSS score
- The timed 25 foot walk, 9-hole peg test, and PASAT will be performed to obtain an MSFC score

- Serum test for creatinine and BUN
- An MRI of the brain with/without gadolinium contrast will be obtained on a 7T scanner

4.6 DISCONTINUATION OF PROTOCOL-SPECIFIED THERAPY

- N/A

4.7 SUBJECT DISCONTINUATION

Subjects may discontinue the study voluntarily at any time. Subjects may be withdrawn from the study if they are unable to tolerate future MRI scans due to development of any exclusion criteria (later implantation of a device, development of allergy to gadolinium, become pregnant, etc.).

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:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject 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

N/A

4.9.2 Analysis of Treatment Group Comparability

N/A

4.9.3 Efficacy Analysis *[if applicable]*

a. Primary Endpoint: Reduction in the number of enhancing leptomeningeal foci on 1 year follow up compared to baseline in MS patients treated with ocrelizumab.

A Wilcoxon signed rank test will be used to determine if there is a significant difference in the number of enhancing foci at baseline versus at 1 year follow up.

b. Secondary Endpoints

Secondary Endpoint: Reduction in the proportion of participants with meningeal enhancement after treatment with ocrelizumab compared to pre-treatment baseline.

Other:

- Reduction in the volume of contrast enhancement on follow up compared to baseline.

- Difference in the proportion of those with no clinical evidence of disease activity (no relapses or disability progression) in participants who experience a reduction in enhancing leptomeningeal foci after treatment with ocrelizumab versus those who do not.

- Difference in the proportion of those with no new cortical lesions on 1 year follow up scans in participants who experience a reduction in enhancing leptomeningeal foci after treatment with ocrelizumab versus those who do not.

Chi-square testing will compare the proportion of participants with leptomeningeal contrast enhancement after treatment with ocrelizumab to the same proportion at baseline. A similar analysis will also test for differences in the proportions of those with no clinical evidence of disease activity and no new cortical lesions in participants who do experience a reduction in leptomeningeal contrast at follow up compared to those who do not.

4.9.4 Safety Analysis

N/A

4.9.5 Missing Data

Any participants with critical missing data (i.e. 7T MRI, EDSS score) will be removed from the final analysis.

4.9.6 Determination of Sample Size

The sample size was calculated based on our preliminary data suggesting that MS subjects with leptomeningeal enhancement will have a mean of 2.27 (sd 1.45) foci per subject at baseline. In order to observe a 50% reduction in the number of foci (at 80% power) on a follow-up scan amongst those with enhancement, 13 subjects would be needed with an α=0.05. To account for the potential of 20% drop-out after screening, the target for recruitment will be 16 participants that meet screening criteria. Our preliminary data suggests that 76% of enrollees with MS will have at least one focus of leptomeningeal enhancement at baseline, necessitating the need for a minimum of 22 subjects to be screened.

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

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 ocrelizumab 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, including signs or symptoms associated with multiple sclerosis that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- 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 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 AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA,

appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study procedures and ends 30 days following the last study procedure or study discontinuation/termination, whichever is earlier.

Assessment of Adverse Events

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

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

Yes

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

No

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

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

5.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

The following questions will be asked at each study visit, in order to elicit adverse event symptomatology:

- "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. Pregnancy

If a female subject becomes pregnant while receiving ocrelizumab or within 90 days after the last dose of ocrelizumab, 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).

f. 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.

g. Case Transmission Verification of Single Case Reports

The Parties will ensure that all single case reports have been adequately received by Genentech, via the study PI emailing Genentech a periodic line-listing documenting single case reports sent by the study PI to Genentech in the preceding 3 months.
Confirmation of receipt should be received within the time period mutually agreed upon.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the study PI 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.

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 the Product. There are no Adverse Events of Special Interest for ocrelizumab.

The non-drug specific AESI's are:

- 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 ´ ULN in combination with total bilirubin > 2 ´ ULN
    - Treatment-emergent ALT or AST > 3 ´ ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, 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. Adverse Event Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

650-238-6067

Email: usds_aereporting-d@gene.com

- **SADRs**

Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

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

- **AESIs**

AESIs requiring expedited reporting shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Non-serious AEs**

Non-serious AEs shall be transmitted to Genentech/Roche on a periodic (e.g., monthly) line-listing containing the following elements (Protocol number, Patient ID, Patient birth date, Adverse Event/MedDRA term, Seriousness of event, Onset date of event, Death date, Product received, Date of first dose, Cause(s) of event, Adverse Event description).

[Note: For special situation reports and non-serious AEs, line-listings are acceptable format. Where the Sponsor sends all cases via the line-listings, the seriousness of the event should be indicated.]

- **Pregnancy reports**

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech 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.

Special situation reports

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

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, 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)
- Lack of therapeutic efficacy

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.

Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

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

5.4 MedWatch 3500A Reporting Guidelines

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

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- 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)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsFo rms/Forms/UCM048334.pdf

5.5 Additional Reporting Requirements for IND Holders

N/A

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 STUDY COMPLETION

The following materials are requested by Genentech when a study is considered complete or terminated:

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

the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

- Email : ocrelizumab-iis-d@gene.com

6.3 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative 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 or the subject's legally authorized representative. 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 by study monitors at any time.

6.4 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.

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 Investigator Brochure 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., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 STUDY MONITORING REQUIREMENTS

There is no DSMB for this study. Any study related adverse events will be reported to the local IRB.

6.6 DATA COLLECTION

Describe methods for data collection.

6.7 STUDY MEDICATION ACCOUNTABILITY (IF APPLICABLE)

If study drug will be provided by Genentech, accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log.

All expired, partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

6.8 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)

6.9 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Genentech will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

REFERENCES

1. Howell OW, Reeves CA, Nicholas R, et al. Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis. Brain 2011;134:2755-2771.

2. Howell OW, Schulz-Trieglaff EK, Carassiti D, et al. Extensive grey matter pathology in the cerebellum in multiple sclerosis is linked to inflammation in the subarachnoid space. Neuropathol Appl Neurobiol 2015;41:798-813.

3. Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol 2004;14:164-174.

4. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 2007;130:1089-1104.

5. Magliozzi R, Howell OW, Reeves C, et al. A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. Ann Neurol 2010;68:477-493.

6. Fukuoka H, Hirai T, Okuda T, et al. Comparison of the added value of contrast-enhanced 3D fluid-attenuated inversion recovery and magnetization-prepared rapid acquisition of gradient echo sequences in relation to conventional postcontrast T1-weighted images for the evaluation of leptomeningeal diseases at 3T. AJNR Am J Neuroradiol 2010;31:868-873.

APPENDIX A

Study Flowchart

Event	Visit 1 (Pre-ocrelizumab)	Visit 2 (after 1 year on ocrelizumab)
Informed Consent	X	
Demographic and clinical data collection	X	X
EDSS[1] examination	X	X
MSFC[2] exam	X	X
Blood draw for creatinine and blood urea nitrogen (BUN)	X	X
7T MRI[3]	X	X
Review of 7T imaging and elimination of participant if no leptomeningeal enhancement see on baseline scan	X	

1. EDSS = Kurtzke Expanded Disability Status Scale score, determined by neurological examination
2. MSFC = Multiple Sclerosis Functional Composite score, determined by administration of Timed 25 foot walk, 9 hole peg test, and PASAT
3. 7T MRI = 7 Tesla MRI of the brain with/without gadolinium contras

APPENDIX B

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: Fax: 650-238-6067

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

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET