PROTOCOL

STUDY TITLE:	Effect of Ocrelizumab on Neuroinflammation in Multiple Sclerosis as Measured by ^{11}C-PBR28 MR-PET Imaging of Microglia Activation
STUDY DRUG:	OCREVUS (ocrelizumab)
SUPPORT PROVIDED BY:	Genentech, Inc.
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1. INTRODUCTION

Cortical demyelination and diffuse white matter (WM) axonal injury are well-established neuropathological features of multiple sclerosis (MS), and main substrates of disease progression[1].

A series of neuropathological examinations of ex vivo progressive MS cases reported that cortical demyelination frequently appears to be topographically associated with meningeal ectopic inflammatory infiltrates of B cells, accompanied by profound cortical microglia activation[2-4]. The extent of meningeal inflammation correlated with microglia activation and the severity of demyelination in the underlying cortex. These findings suggest that cortical demyelination in MS may be induced by soluble factors, produced within those B cell follicle-like structures, which then diffuse from the meninges into the cortex and trigger demyelination directly or indirectly through activation of microglia. Meningeal inflammation, in association with cortical demyelinating lesions, has also been described in biopsies at MS onset[5].

Neuropathological studies implicate that inflammation, through activation of microglia, may also represent a relevant pathogenic factor in the development of diffuse white matter (WM) axonal injury[6].

Ocrelizumab, a humanized monoclonal antibody targeting the CD20 marker in B cells, has been recently shown to have beneficial effects in relapsing-remitting MS (RRMS), but also in primary-progressive disease (PPMS) by significantly reducing new CNS inflammation, relapses, and progression in patients with gradually worsening disease[7, 8]. The efficacy of Ocrelizumab in MS challenges our understanding of MS disease-mechanisms, suggesting that B cells may have a main role in disease pathogenesis by contributing to propagate neuroinflammation within the MS CNS. It appears likely that functionally distinct B cells contribute to MS disease process through diverse mechanisms within the distinct disease compartments, and throughout stages of MS[9]. Peripheral pro-inflammatory B cells play and important role in relapsing disease mechanisms[10], whereas meningeal collections of B cells potentially participate in the maintenance and propagation of CNS-compartmentalized disease.

Neuroinflammation by means of microglia/macrophages activation can be imaged in vivo on positron emission tomography (PET) using selective radiotracers that bind to the 18kDa translocator protein (TSPO), a protein that is upregulated in activated microglia/macrophages[11]. In a cross-sectional study, using simultaneous magnetic resonance-PET (MR-PET) imaging with ^{11}C-PBR28, a second-generation TSPO radiotracer, we demonstrated abnormally high TSPO expression, indicative of microglia/macrophages activation, across the brain of MS cases[12]. Relative to healthy controls, the greatest TSPO increase was found in the cortex and cortical lesions, thalamus, hippocampus, and normal appearing WM (NAWM). Additionally, in MS increased ^{11}C-PBR28 binding in cortex, deep GM, and NAWM correlated with neurological disability and impaired cognitive performance. We have developed a method for estimating ^{11}C-PBR28 uptake that does not require arterial sampling and shows the same sensitivity as quantitative blood analysis to ^{11}C-PBR28 changes in MS[12, 13].

2. OBJECTIVES

In this study, we propose to evaluate, serially, functional and structural tissue changes in the cortex and WM of subjects with RRMS and progressive disease under Ocrelizumab using ^{11}C-PBR28 MR-PET. The overall goal of the study is to

use advanced imaging protocols to determine the effect of ocrelizumab treatment on neuroinflammation as measured by microglia activation.

2.1 PRIMARY OBJECTIVES

To assess whether treatment with Ocrelizumab in subjects with either RRMS or progressive MS is associated with decreased ^{11}C-PBR28 binding in the 1) cortex, and 2) WM (lesions and normal appearing WM, NAWM), suggesting reduced neuroinflammation.

2.2 SECONDARY OBJECTIVES

To assess whether changes in neuroinflammation under Ocrelizumab treatment, as measured by ^{11}C-PBR28 uptake at either 12-month follow up relative to the baseline, are associated with changes in structural MR metrics of brain tissue damage including WM lesion load, cortical atrophy and demyelination in the cortex and in the NAWM as measured by magnetization transfer ratio (MTR).

To explore whether changes in functional and structural imaging metrics under Ocrelizumab are associated with changes in clinical outcomes measures (EDSS, SDMT, MSFC).

3. STUDY DESIGN

Open-label, serial longitudinal study on 24 MS patients (with RRMS or progressive MS1) fulfilling the inclusion/exclusion criteria detailed below.
MS patients will be recruited through competitive enrollment at Massachusetts General Hospital (Dr. Eric Klawiter) and Beth Israel Medical Center (Dr. Jacob Sloane). Enrolled MS subjects will be scanned at MGH at baseline (pre-treatment) and at 12-month after Ocrelizumab therapy on an integrated MR-PET scanner using ^{11}C-PBR28 produced on site.

3.1 DESCRIPTION OF THE STUDY

This is a prospective open-label study in which we will enroll 24 subjects with MS, including patients with a relapsing-remitting type of MS (RRMS), and subjects with a progressive type of MS (PMS). MS subjects fulfilling the inclusion criteria detailed below, and deemed by their referring clinician to be suitable for treatment with Ocrelizumab as part of their standard medical care, will be enrolled in the study. Women who are of childbearing potential and believe they may possibly be pregnant will not participate in the study.
At the first visit, subjects will be screened and the study procedures will be explained to subjects in detail. Subjects will be asked to review the consent form, and any questions they may have will be answered.

Screening visit and consenting

Subjects who fulfill demographic and clinical inclusion criteria of the study will undergo routine clinical evaluations at baseline. MR contraindication screening will also be done to ensure that they meet also the basic imaging

inclusion/exclusion criteria for the study procedures. For the MR contraindication screening, the standard Martinos Center subject screening form will be administered. During screening, potential participants will be fully informed of the purpose and activities involved in the research study. Interested subjects will be scheduled for an in-person visit where written informed consent will be immediately obtained by a licensed physician investigator or a nurse practitioner, prior to initiating any of the study procedures. At the time the registered nurse practitioner obtains consent, each subject will be offered the option to speak with a physician investigator.
Soon after consenting subjects will undergo a history and physical assessment, and blood drawing for TSPO genotyping. Subject screening visit and consenting may take place either on the same day or as a separate visit.

PBR affinity test
While ^{11}C-PBR28 has the advantage of binding to the TSPO protein with a higher ratio of specific-to-nonspecific binding than ^{11}C-PK11195, it also present a potential limitation, in that about 10% of human subjects show no binding to PBR28[14]. It has been demonstrated that a common polymorphism (rs6971) in the TSPO gene, which leads to an aminoacid substitution (Ala147Thr), predicts PBR28 binding affinity in human platelets[15]. Since the low-affinity binder phenotype is consistent across all tissues within the same subject, testing for the Ala147Thr polymorphism has been suggested to predict low affinity for 11C-PBR28 in all organs, including the brain. Thus, all subjects considered for potential participation in a ^{11}C-PBR28 scan will be genotyped for the Ala147Thr TSPO polymorphism. Venous blood (~10 ml) will be drawn into EDTA-containing tubes for Genomic DNA.
High or Mixed affinity binders (Ala/Ala or Ala/Thr) will be considered eligible, whereas the Low affinity binders (Thr/Thr) will be considered ineligible for the study.

MR-PET scan
MR-PET imaging will be performed at baseline (pre-treatment) and at 12-month follow up after initiating therapy with Ocrelizumab.

On the day of each MR-PET scan, before starting any imaging procedure, women of childbearing age will be tested for pregnancy using a blood pregnancy test. If the test performed comes back positive for pregnancy or the subject is breastfeeding, the subject will not undergo any of the PET procedures.

Prior to radiotracer injection:
1. The procedure will be explained to the subject and any questions he/she has about the procedure will be answered.
2. Subject information such as height, weight will be obtained.
3. All subjects will undergo a MR-PET scan using ^{11}C-PBR28.
4. Prior to injection of ^{11}C-PBR28 patients will be asked to urinate to minimize the possibility that they will need to move during the scan.

Radiotracer injection:
1. Radiotracer injection may occur either outside or inside the MR-PET scanner. The subjects will be positioned on the MR-PET scanner table with their head in the center of the field of view; support devices under the back and/or legs will be used to enable the patient to comfortably maintain his/her position throughout the scan.
2. ~12 mCi of ^{11}C-PBR28 will be injected and the time of injection will be recorded.

Post-scan procedures:
1. The subject will be asked to void again immediately after the scan and he/she will be counseled on the importance of continuing to drink fluids for several more hours. This will increase urine flow rate, which will help minimize the radiation dose to the bladder wall.
2. A detailed information sheet on post PET scan procedures will be given to the subject.

Data acquisition: Subjects will be positioned in the BrainPET scanner and data acquisition may start after an intravenous bolus injection of ^{11}C-PBR28 (~12mCi) to capture the 60-90 minutes after radiotracer administration.
During PET acquisition, the following MR protocols will be simultaneously acquired: 1) standard FLAIR protocols for WMLV estimation; 2) T1 anatomical images for Freesurfer cortical reconstruction and coregistration with MR-PET and 7T data (~7 min); standard MTR protocols (~16 min).

Data analysis: Standardized uptake value (SUV) maps of ^{11}C-PBR28 uptake will be created for 60-90-minute PET frame and resampled at 1.25 mm isotropic voxels, as previously detailed[12]. Data in MS and in other neurological disorders show that ^{11}C-PBR28 SUV can substitute for, and may even be more sensitive than absolute quantitation[12, 16, 17]. This method is expected to improve subject tolerability by allowing shorter scan time and not requiring arterial catheterization. In addition, the method allows smaller sample sizes for comparable statistical significance because of the relatively low variability of SUV. Scan-rescan reproducibility data in 5 healthy subjects at our Center demonstrate that quantification of ^{11}C-PBR28 SUV normalized by a reference region (SUVR) has excellent stability over time, with mean±SD SUVR test-retest % change in all regions tested of 0.1±1.16, and with coefficient of variations across brain regions below 10%.
Using a surface-based analysis, all subjects in this study will have acquired 3T anatomical and MTR maps to estimate intracortical MTR at 50% depth from the pial surface. With those 3T maps, specifically the relationship between the extent of microglia and/or macrophages activation and changes in MTR will be investigated. Decreases in MTR would suggest a reduction in cortical myelin content. Furthermore, this study will include whether changes in MTR in WM lesions or normal appearing WM (NAWM) is accompanied by changes in microglia/macrophages activation as measured by ^{11}C-PBR28 MR-PET or whether these processes are unrelated.
Finally, the relationship between radiographic measures from MR-PET studies and clinical outcome measures will be assessed.

Clinical assessment.
Clinical outcomes will be collected at baseline and at 12-month intervals. EDSS will be formally determined at baseline and 12 months as a descriptor of patient characteristics but not as an outcome measure. Clinical outcomes will include a modified MS Functional Composite (7 scores total) including the 25 foot walking time (25FT) and 6 minute walk (6MW) (2 scores), 9 Hole Peg Test (9HPT) (right and left separately; 2 scores), Symbol Digit modality test oral version (SDMT) (1 scores) and the Sloane Low Contrast Sensitivity Chart (SLCC) at 2.5 % (OD and

OS separately; 2 scores). All tests will be administered 2 times prior to baseline to minimize learning effects and always administered under standardized testing conditions with scores discarded if unreliable (eg right hand in a cast would lead to discarding the RUE 9HPT score). Worsening will be defined as a > 15% change on the 25FT, 6MW or 9HPT or a decrease of > 5 points on the SDMT or > 3 points on the SLCC; sustained worsening will require persistence of this magnitude of change for at least 6 months. Worsening may be initiated in the setting of a relapse but will still require persistence to meet sustained disability criteria. Relapses will be defined as the development of new neurological symptoms lasting for at least 48 hours associated with new or worsening findings on examination in the absence of a febrile illness or other potential comorbid condition.

3.2 RATIONALE FOR STUDY DESIGN

A large body of evidence shows that B cells play a main role in disease pathogenesis and progression in multiple sclerosis, both in the gray matter and in the WM. In the gray matter, the cortex is a main target of demyelination and neuroaxonal loss and this pattern of pathology is constantly associated with disease progression[1]. Neuropathological data demonstrate that cortical demyelination is largely driven by meningeal inflammation, often organized in lymphoid-like B-cell structures, through the activation of microglia[2-4]. Several studies also show that the extent and severity of cortical demyelination correlate with the degree of microglia activation. In the normal appearing WM, diffuse microglia activation is closely associated with axonal loss. Treatment with Ocrelizumab, a monoclonal antibody that targets the CD20 expressing B cells, has shown to be beneficial in RRMS and PMS by reducing CNS inflammation, relapses, and progression in patients with gradually worsening disease[7, 8]. Inflammation in the brain has been assessed, however, using traditional MRI methods including gadolinium enhancing lesions and new T2 lesions. These methods are insensitive to detect cortical inflammation, as well as the compartmentalized inflammation that typically characterizes progressive MS. Additionally, neuroinflammation by means of microglia/macrophages activation can be present in the absence of significant blood brain barrier abnormalities, or even precede them[18]. Here we propose to study the effects of Ocrelizumab treatment on neuroinflammation using a sensitive and reproducible method that we have implemented in our Lab.

3.3 OUTCOME MEASURES

Make sure the primary and secondary outcome measures are consistent with the study design and objectives. The items listed below should be considered when specifying the outcome measures; they should be discussed if necessary to justify the study design:

- Appropriate timing in terms of follow-up. The intervening length of time between assessments of response affects time outcomes and the statistical analysis.

- Best measure of response (e.g., duration of response, incidence of toxicity, etc.)
- Clinical applicability (e.g., consider whether the outcome measures are clinically meaningful and contribute to patient benefit)

  If necessary, explain why these outcome measures were chosen (i.e., medical justification)

3.3.1 Primary Outcome Measure

^{11}C-PBR28 uptake measured as standardized uptake values (SUV, mean radioactivity/injected dose/weight) from the 60-90 minutes post-injection data) and normalized by a pseudoreference region (SUVR) as previously detailed. Tracer uptake will be assessed in 1) cortex; 2) WM lesions; 3) NAWM.

3.3.2 Secondary Outcome Measures

Cortical thickness.
WM lesions.
Cortical MTR.
NAWM MTR.

3.3.3 Ancillary Safety Outcome Measures

NA

3.4 SAFETY PLAN

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

Ocrelizumab-related infusion reactions will be managed by the treating physician as detailed in Section 4.3.2 and according to recommended guidelines by the U.S. Food and Drug Administration (FDA) and Good Clinical Practices (GCPs), and as part of the patient standard clinical care. All laboratory analyses related to Ocrelizumab safety will also be conducted in patients as part of their standard medical care and supervised by their referring clinician.
As part of this study, enrolled MS subjects will be asked to fill out a monthly questionnaire to report any new medical event or change in treatment. A designated investigator/clinical research coordinator in the study will review periodically the questionnaire with the referring clinician to record possible adverse events.

MR-PET safety assessment: During the MR-PET scans subjects will lie motionless on the MR table, which will slide into the narrow tube of the MR-PET. Subjects will easily be able to hear and speak to the research staff throughout the scan. If they wish, they will be free to stop the examination at any time. The Siemens MR-PET system has also built in self-monitoring system that automatically shuts off if parameters exceed safe levels. For backup protection technicians at the Martinos Center constantly monitor the subjects' physiological signs and the quality of the raw data.

We have a step-by-step checklist of the scan session and safety precautions that the research team follows for every subject. We will also ask patients about their comfort level throughout the session.

The U.S. Food and Drug Administration (FDA) recently gave the regulatory clearance of a hybrid PET/MRI scanner in the U.S. Additionally, FDA considers investigations of MRI software and hardware operating within FDA specific parameters as non-significant risk device studies. All studies will adhere to these (non significant risk) FDA approved safety levels for the Siemens system. These system parameters include static magnetic field, time varying magnetic fields (dB/dt), specific absorption rate (SAR), and acoustic noise levels.
The radiation exposure in this study will be ~ 3.7 mSv per PET scan. If subjects have participated in other research studies in the past 12 months that have involved radiation exposure, they will be asked to inform the investigators or study staff (by placing a check mark on the consent form verifying that they have or have not been exposed to other radiation in the past 12 months). If it is determined that their prior radiation exposure exceeds our current guidelines, it is possible that they will no be allowed to participate in this study.
We will use ^{11}C-PBR28 produced by the cyclotron/radiochemistry/radiopharmacy facility at the A. A. Martinos Center for Biomedical Imaging. We will follow the safety standards approved by the Radiation Safety Committee for the use of radioligands. The IV injection will be administered either by a physician or by a trained technician. Should there be an adverse event, Dr. Mainero will be responsible for communicating with the IRB and Genentech within the stipulated time frame.

The risks of neurological and neuropsychological testing are minimal. Patients with MS routinely undergo neuropsychological testing as part of standard clinical evaluation. As these tests evaluate higher cognitive processes such as executive functioning and memory, subjects may become anxious from self-perceived inability to successfully accomplish the tasks associated with the testing. Subjects will be advised prior to testing that the tasks are designed to be challenging. Appropriate referral to psychiatry/psychology will be provided if necessary.

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

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current 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

24 subjects with either RRMS or PMS.

4.1.2 Inclusion Criteria

- Signed informed consent
- RRMS and/or PMS subtype
- Age between 18-65 years
- EDSS between 0 and 7.0
- Express at least one high-affinity (Ala147) allele of the TSPO receptor for PBR28

4.1.3 Exclusion Criteria

- Hypersensitivity to trial medications
- History of life-threatening infusion reaction to Ocrelizumab
- Acute or uncontrolled chronic medical condition
- Impaired hearing
- Claustrophobia
- 300 lbs or greater (weight limit of MRI table)
- Pregnancy or breastfeeding
- Sensitivity to imaging agents
- Contraindications to MRI
- Use of benzodiazepines, topiramate, doxycycline, mynocicline.

4.2 STUDY TREATMENT

Treatment will not be determined by the protocol and will be administered as per standard of care.

4.3 STUDY ASSESSMENTS

Signed, IRB-approved informed consent must be obtained from patients prior to the pretreatment assessments. Ensure that informed consent be obtained for both the any mandated testing or screening process for this protocol.

The following are recommended evaluations:

IRB-approved informed consent will be read and explained by Dr Mainero or by another co-investigator or study staff to patients during their first visit to the

Martinos Center. We will train research assistant/technologist staff to pre-consent subjects for the study. Those who choose to participate in the study will then meet with Dr Mainero or another co-investigator or study staff to receive a more detailed explanation about the study and the procedure. Patients willing to participate in the study will sign the consent form in the presence of a licensed physician investigator or nurse practitioner. Consent form will explain the purpose of the study, the procedure, the risks and discomfort, and the possible benefits. It will also address the cost and payment issues, and guaranties confidentiality. Each subject recruited to the study will have a file kept in the Martinos Center. Each file will include a copy of the signed consent form.

4.3.1 Assessments during Treatment

The following are recommended evaluations:

- EDSS at baseline and 12-month interval. EDSS will be formally determined at baseline and 12 months as a descriptor of patient characteristics but not as an outcome measure.

- MS Functional Composite (7 scores total) including the 25 foot walking time (25FT) and 6 minute walk (6MW) (2 scores), 9 Hole Peg Test (9HPT) (right and left separately; 2 scores), Symbol Digit modality test oral version (SDMT) (1 scores) and the Sloane Low Contrast Sensitivity Chart (SLCC) at 2.5 % (OD and OS separately; 2 scores) at baseline and 12-month interval.

4.3.2 Follow-Up Assessments

We don't plan to do any follow-up assessment once patients terminate the study or drop-off from the study for any given reason unless the reason for dropping-off is strictly related to potential issues arising from ^{11}C-PBR28 MR-PET imaging. In these cases, follow-up will be followed according to standard IRB recommendations and guidelines.

In cases where discontinuation is due to Ocrelizumab-related reasons, follow-up will be performed by the treating physician as part of their standard medical care.

4.4 SUBJECT DISCONTINUATION

Subjects will be discontinued from the study in case any of the conditions listed in the exclusion criteria. We will evaluate on a case-by-case basis discontinuation of subjects starting treatment with any of the drugs listed in the exclusion criteria, as treatment of these drugs can be temporary and thereby not necessarily affect MR-PET assessments.

4.5 STUDY DISCONTINUATION

Genentech, Study Center, and the Principal Investigator have 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. The enrollment time period will start only after all procedures and protocol will be IRB approved.
- Data recording are inaccurate or incomplete
- Study protocol not followed

4.6 STATISTICAL METHODS

4.6.1 Analysis of the Conduct of the Study

We will follow IRB guidelines to ensure that all study procedures are conducted appropriately.
The principal investigator will have periodic meetings with all study staff to oversee any possible study deviation or violation to the protocol. We have a step-by-step checklist of the scan session and safety precautions that the research team follows for every subject. We will also ask subjects about their comfort level throughout the session.
Dr Mainero or another co-investigator will monitor all MR-PET scanning. Dr Mainero, the PI, and all other study staff (co-investigators and research technicians) are certified in the Partners Health Care System Human Subject Protection Education Requirements and are familiar with the procedures and steps necessary to report adverse events to the IRB committee

4.6.2 Analysis of Treatment Group Comparability

We will have only one treatment group (Ocrelizumab) in which we will assess neuroinflammation by means of ^{11}C-PBR28 MR-PET imaging (SUVR) at 2 time points: 1) baseline, 2) 12-month follow up.
At baseline, patient SUVR across different regions in WM and gray matter will be compared with brain SUVR data from a healthy control dataset obtained at the Martinos Center by using linear regression models and adjusting for age and PBR affinity. Group comparisons (baseline vs 12-month) will be carried out using region of interest analysis or voxelwise approaches by means of paired-test and/or ANOVA. In patients, regression models will be used to determine the relation between SUVR and structural MRI metrics (lesion load, MTR in NAWM and cortex), and adjusting for age and PBR affinity. Multivariate regression models will be also used to assess the relation between SUVR and EDSS at baseline and EDSS change at 1-year follow up, adjusting for PBR affinity. For evaluating changes/drug effects in the cortex and associations between cortical

SUVR and MRI or clinical metrics we will perform vertex-wise surface-based analyses by sampling SUVR maps at mid-cortical depth to reduce partial volume effects. Age and PBR affinity will be included as covariates of no interest when appropriate.

4.6.3 Efficacy Analysis

Not applicable

4.6.4 Safety Analysis

List all safety endpoints (i.e., endpoints relating to adverse events, laboratory assessments, physical examinations, vital signs, or any special safety assessments). Variables relating to adverse events might include timing, severity, relationship to drug, relationship to therapy, outcome, effect on therapy, and degree of seriousness.

Indicate the subject groups (usually all subjects) to be used in analyzing the safety variables.

Unless specific safety questions have been included in the study objectives (and an appropriate sample size and study design have been established to permit answering those questions), it is usually sufficient to use descriptive procedures for summarizing safety data.

4.6.5 Missing Data

Data analysis will be conducted even in the case of missing data by considering separately each time point. We will consider missing data all the metrics that are not acquired within 3-months of the expected time point.

4.6.6 Determination of Sample Size

Quantification of ^{11}C-PBR28 uptake shows excellent scan-rescan stability.

In 5 healthy controls (2 with high affinity binding, HAB, and 2 with mixed affinity binding, MAB for PBR28) we assessed the 3-month scan-rescan stability of 60-90 minutes ^{11}C-PBR28 SUVR quantification across all cortical regions sampled at mid-cortical depth (50% depth from pial surface). Results show excellent stability of these measures over time, with mean±SD SUVR test-retest % change in all regions tested of 0.1±1.16, and with coefficient of variations (COV) across cortical regions below 10%. An example of test-retest 60-90 minutes SUVR in the fusiform gyrus and medial prefrontal cortex from 5 healthy subjects is illustrated in **Fig. 1.**

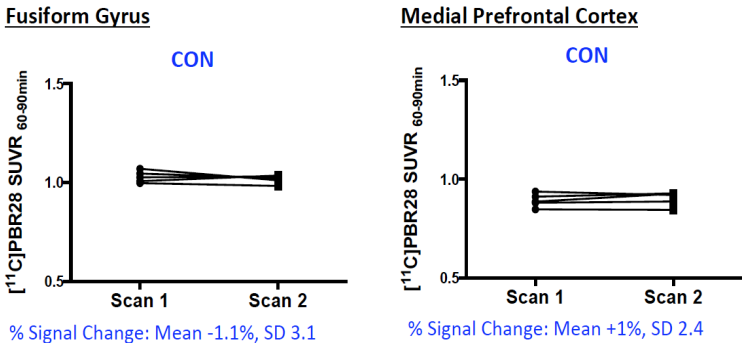

Fig. 1. Plots illustrate mean % signal change of test-retest 60-90 minutes ^{11}C-PBR28 SUVR in the fusiform gyrus and in the medial prefrontal cortex in 5 healthy controls that underwent ^{11}C-PBR28 MR-

^{11}C-PBR28 uptake. We found an increase in ^{11}C-PBR28 uptake in cortical lesions of ~26% in 13 RRMS and of ~29% in 14 SPMS[12], and a variability in ^{11}C-PBR28 uptake of ~10% among subjects. By assuming a variability among subjects of ~10-20%, we have a 90% power (significance level of 5%) to detect an absolute difference in ^{11}C-PBR28 uptake between MS and HC of ~15%. From scan-rescan changes in ^{11}C-PBR28 uptake around ~1%, we anticipate to have a 90% power to detect at least a 1.5% longitudinal change of values over time.

4.7 DATA QUALITY ASSURANCE

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

5. SAFETY 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 standard medical care 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 MS 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 radiotracer injection).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

- An AE should be classified as an SAE if 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 may be 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 treatment and ends 30 days following the last administration of radiotracer and MR-PET or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through 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.

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 subject evaluation timepoints should be adopted. Examples of non-directive questions include:

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

Specific Instructions for Recording Adverse Events

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

a. Diagnosis vs. Signs and Symptoms

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

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or

contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

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

d. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living[a]

3 Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self care activities of daily living[b,c].
4 Life-threatening consequences or urgent intervention indicated[d]
5 Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 6 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to 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 study drug 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).

g. Post-Study Adverse Events The investigator must report any SAE they might become aware of occurring after a subject has completed or discontinued study participation if attributed to prior ocrelizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

h. 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 via The Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by The Sponsor to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

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

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

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

i. AEs of Special Interest (AESIs)

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

There are no ocrelizumab Events of Special Interest.

Adverse events of special interest for this study may 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 x ULN in combination with total bilirubin > 2 x 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

j. Exchange OF SINGLE CASE REPORTS

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

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

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be reported to:
PC Hotline Number: (800) 334-0290

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

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

SADRs
Serious AE reports that are related to the Product 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 shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Special Situation Reports
Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), 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.

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

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

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

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

MEDWATCH 3500A REPORTING GUIDELINES

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

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)

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

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

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

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Dr. Mainero as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the European Medicine Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Dr. Mainero as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable

Dr. Mainero, as the PI of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has been filed an IND in compliance with local regulations.

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

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

Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of ocrelizumab. An unexpected adverse event is one that is not already described in the ocrelizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech/Roche within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of ocrelizumab. An unexpected adverse event is one that is not already described in the ocrelizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech/Roche, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech/Roche Drug Safety:

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

And The Sponsor will be responsible for the distribution of safety information to Site IRB:

FAX (857) 282-5693
Telephone (857) 282-1900

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

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

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at:
Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Other Reports

The Sponsor will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

Study Close-Out

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

ocrelizumab-iis-d@gene.com

And to Genentech Drug Safety CTV oversight mail box at:
ctvist_drugsafety@gene.com

QUERIES

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

SAFETY CRISIS MANAGEMENT

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

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

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 or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- 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

All study procedures of 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

NA

6.6 DATA COLLECTION

Data collection will be carried on in the forms of imaging data and demographic/clinical data and/or questionnaire as detailed in the protocol. All data will be kept at the Martinos Center and accessible only to study investigators.

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.

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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