PROTOCOL

STUDY TITLE:	A single-center prospective measurement of upper extremity function in multiple sclerosis patients with advanced disability treated with Ocrevus™
STUDY DRUG:	OCREVUS (ocrelizumab)
SUPPORT PROVIDED BY:	Genentech, Inc.
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STUDY NUMBER:	OCRE-UP
PROTOCOL VERSION/DATE:	4.1 / 10JAN2020

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) that affects approximately 2.5 million people worldwide. It is a chronic condition characterized clinically by focal disorders of the optic nerves, brain and spinal cord, which remit to a varying extent and recur over a period of many years. Most patients eventually experience progression and accumulation of symptoms which can include profound muscle weakness, impaired gait and mobility, bladder and bowel dysfunction, cognitive and visual impairments and sexual dysfunction [1].

In patients that have disability that involves the upper extremity, this can lead to loss of independence in activities of daily living such as dressing, feeding and hygiene [2]. Upper extremity(UE) strength is also important for a patient being able to independently shift weight in a wheelchair, maneuver an electric wheelchair, and change position in bed, thus minimizing risk for decubitus ulcers. As opposed to lower extremity function, a very small loss of strength and function can translate into significant changes in functional independence. The loss of independence then impacts quality of life (QoL) for both the patient and the caregiver(s).

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

To measure for clinical stabilization (defined as no significant change (≤20%) from baseline of UE function in multiple sclerosis patients with upper extremity impairment treated with Ocrevus™.

2.2 SECONDARY OBJECTIVES

To evaluate the relationship between UE function (objective and subjective) and fatigue, cognition and QoL.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Ocrevus™ is the first FDA approved disease-modifying treatment for primary progressive MS as well as relapsing MS [3]. In the clinical trials considered by the FDA (OPERA I/II, ORATORIO), the highest Expanded Disability Status Scale (EDSS) included in the participants was 5.5 (OPERA I/II) and 6.5 (ORATORIO) [4]. The EDSS score is heavily weighted on walking ability and is not a useful measurement for UE function [5,6]. The primary endpoint in the primary progressive MS trial with Ocrevus™ was EDSS and in the relapsing MS studies, EDSS was used as a secondary endpoint. The Multiple Sclerosis Functional Composite (MSFC) score (Z score), a composite of quantitative measure of walking speed, upper limb coordinated movement (9 Hole Peg Test/9HPT) and cognitive function, was obtained as a secondary clinical

measure with scores being favorably higher in patients treated with Ocrevus™ (OPERA I/II).The z score, however, is not very useful in delineating which of the three clinical functions was maintained or showed less progression given that three domains are included in the score [7,8,9]. Data presented recently from the Oratorio trial analyzed the intention to treat population of PPMS patients and the subgroups of patients with upper extremity functional impairment using the 9HPT; results demonstrated reduction in risk of clinical progression in upper extremity disability in patients treated with Ocrevus compared to placebo. There was improvement in the change from baseline to week 120 in 9HPT time in treated patients. Abnormal baseline 9HPT was defined as >25 seconds and upper extremities were defined as “better hand” and “worse hand”, each individually tested, with clinical progression determined at 12 and 24 weeks in 3 sub-categories of progression: lengthened time of 9HPT >15%, >20% and 25%. [10]

In our study we aim to not only replicate the results in the Oratorio trial with upper extremity dysfunction, but also widen the spectrum of patients that may benefit (given an expanded MS population of patients, not exclusive to PPMS and widen the range of potential disability that the patients may have (broader EDSS rage 4-8). We anticipate that by using a test that better emulates activities of daily life performed with the upper extremity, such as the TEMPA (Test d’Evaluation de la performance des membres Superieurs e Personnes Agees) we will obtain more real life application of the benefits of receiving treatment with Ocrevus, and anticipate that patients can maintain the function they have or potentially improve function.

3.2 RATIONALE FOR STUDY DESIGN

We anticipate the use of Ocrevus™ in patients with progressive disease which includes those with advanced disability, regardless of a dearth of data to guide the prescriber regarding its effect in this population. The rational for this study is to gain information which will help the prescribers of Ocrevus™ answer the question “Will Ocrevus™ help me if I have hand or arm weakness?” especially if posed by a more advanced MS patient (EDSS 4.0-8.0 with UE involvement) than those included in the clinical trials. In previous trials (ORATORIO), the included patients were only those diagnosed with primary progressive MS and their entry EDSS was of a lower disability range (3.0-6.5) than those proposed in this study. Therefore, the results cannot be completely extrapolated to the population of multiple sclerosis patients with more advanced disability that we propose to study. We aim to identify MS patients that have weakness in at least one upper limb, knowing that delaying disability affecting the functional use of the UE will help patients remain independent for some activities of daily life and will contribute to an improved quality of life.

The importance of choosing validated upper limb outcome assessment tools cannot be emphasized enough. The Nine-Hole Peg Test (9HPT), an objective measure of manual dexterity, which is incorporated into the MSFC, is a widely used measure across most clinical trials in multiple sclerosis populations.

The EDSS is an ordinal scale of neurological disability designed specifically for MS patients and will provide specific quantitative measure of upper limb strength, sensory impairment and ataxia of the upper limb with each Functional System Subscore. This score will aid in deciphering limitations due to tremors or ataxias.

The Test d'Evaluation de la performance des Membres Supérieurs des Personnes Agées (TEMPA) has been previously studied for validity in clinical trials and specifically in multiple sclerosis patient populations and there was a strong correlation between the TEMPA and 9HPT. [11, 12] The TEMPA consists of 9 tasks that mimic tasks of daily living such as picking up a jar, pouring water from a pitcher, handling coins, writing on an envelope and opening a pill container, as examples. The tasks are assessed by a rater by measuring speed of execution (seconds) and by functional rating of the subject's independence in performing them using an ordinal scale of 0 (completed without difficulty) to -3 (could not complete the task). The test provides a unilateral and bilateral score and evaluates different grasp, grip and pinch functions. Obtaining baseline scores and sequential measurements will allow us to graph scores over time for each patient and assess the change. This type of testing would give us a clear picture of any changes in UE functionality and would highlight meaningful clinical data that would be easily translated to patients- stability of function vs clinical progression >20% change from baseline. This key data would be a helpful reference when discussing starting treatment with Ocrevus™ in this population of patients.

The normative values available for the TEMPA were obtained in the elderly (ages 60-80, men and women). The speed of execution of the 9 tasks in each hand takes about 70 to 80 seconds to complete in this population. [12]
When one reviews the validity study of the TEMPA in MS patients [average EDSS was 7 and age median was 46 years old], this same parameter took them between 100 and 400 seconds [1 and 1/2 to 6 minutes] to complete.

Schwid et al in 2002 showed that MS patients did not vary from their baselines in performing the 9HPT by >20% day-to day and therefore the if there was change measured >20% from their baseline this was stipulated to indicate change in function [13].
In a pilot study where a technology enhanced training program for improving upper limb muscle strength in MS patients the TEMPA was used at baseline and 8 weeks later, and there was a trend towards statistical significance of improvement in function with TEMPA change of 20 to 40 seconds [14].
Since the 9HPT and TEMPA have been show to correlate and there are numerical values measured in both, we plan to emulate the Oratorio study and look at >15%, >20% and >25% [in better hand and in worse hand] change from baseline with increases in time implying clinical progression and stability or decrease in time implying stability or improvement in function.

The Jamar dynamometer is validated tool often used by occupational therapist to measure grip strength [15]. Grip strength is an important part of daily living tasks and can give clinicians insight into patient restrictions and clinical changes.

The Upper Extremity Functional Index (UEFI)is a self-report questionnaire that has been found reliable, valid and sensitive as a patient- reported outcome measure tool for quantifying UE function rated on a 5-point Likert scale This 20-item measure is recommended in research and clinical setting due to its uni-dimensionality: it measures only UE function [16,17]. Scores range from 0 to 60 with lower scores indicating more functional difficulty. It has been used in several studies in patients with musculoskeletal upper extremity problems, to include patients with MS, and UEFI scores correlated with mean 9-HPT scores. [18] We anticipate that patients in our study will have perceived stabilization of their upper extremity function and plan to use the UEFI to measure this by means of its validated 9 points of change from baseline for minimal detectable change in function.

The Symbol Digit Modalities Test (SDMT) is a validated measure used to assess mental processing speed in MS clinical trials and has an oral response version. There is evidence that cognitive measures may correlate with upper extremity function. This can possibly be explained by a cerebral relationship between motor function and cognition [19]. As a secondary measure we will collect SDMTs at each visit to explore correlations with upper extremity function, as well as QoL measures.

The natural history of progression of disability in MS is foreseeable in a 2-year span period and this is evident when one examines the placebo population in the recent Oratorio trial; obtaining these measures over a 2-year period aims to observe stability of the upper limb function with Ocrevus™ treatment.

3.3 OUTCOME MEASURES

- The UE function will be assessed every 6 months over 24 months to gauge for any small changes at certain intervals but to also have a sufficient length of time that can be compared in order to assess for any type of change over time. *
- Incidence of UE functional changes (improved, worsening or stable) with scores of time and performance on the TEMPA.
- In this group of patients (advanced disability) there is less concern with relapse rate reduction; relapses happen at a low rate. There is more concern regarding any loss of function, and we will focus on UE function. Studies like this would provide better data for this type of patient aiding in the process of selecting appropriate disease modifying therapy.

*UE function includes measures on the TEMPA, UEFI and 9HPT.

UEFI is subjective and answered by the patient. The Upper Extremity Functional Index (UEFI) is a self-administered questionnaire which measures disability in patients with upper extremity conditions. The questionnaire lists 20 activities and the patient gives a score to each based on the difficulty they have completing that activity. The scores given to the 20 questions are added to give a highest possible score of 80. The lowest possible score is 0. A lower score indicates that the person is reporting increased difficulty with the activities as a result of their upper limb condition. The change from baseline per patient and for group means will be analyzed. A clinically significant change is determined as a 12% change. [20]

The TEMPA scale is composed of nine standardized tasks which represents activities of daily living. Four items are unilateral (pick up and move a jar; pick up a pitcher and pour water into a glass; handle coins; pick up and move small objects) and five bilateral tasks (open a jar and take a spoonful of coffee; unlock a lock and open a pill container; write on an envelope and stick on a stamp; shuffle and deal playing cards; put a scarf around one ’s neck). The outcome parameters used in this study are speed of execution (seconds) and the functional rating. The functional rating refers to the participant’s independence in each task measured on a four-level scale: (0) successfully completed without hesitation or difficulty; (-1) completed, but with some difficulty; (-2) partially executed or some steps were performed with significant difficulty; and (-3) not completed, even if any degree of assistance was offered. A total score will be determined by adding the scores obtained for both the unilateral and bilateral tasks. Individual analysis of the unilateral and bilateral scores will be conducted to evaluate for functional improvement in the affected UE. Scores typically range from 0 to -50, with higher scores representing better performance. [12] The UE function will be measured by a consistent rater that is trained and qualified (must be a MD or equivalent).

The 9HPT is an objective measure of manual dexterity, which is incorporated into the MSFC, is a widely used measure across most clinical trials in multiple sclerosis populations. The time to completion is measured twice on both the dominant and non-dominant hand. For this study purpose will also record the “better” and “worse” limb so that the data can be cautiously compared to prior studies completed in multiple sclerosis patients. The task of the 9HPT is for the patient to pick up each individual peg, one at a time, and place it in the board (that has the same number of peg holes for each peg). Once all the pegs are placed in the peg holes the patient then removes each peg, again one at a time, placing them back into the peg bowl from which they were originally located. Although this measure has been used in several multiple sclerosis trials due to its ease of administration, there are many other factors of upper extremity function that are not being assessed that can be captured by the TEMPA.

3.3.1 Primary Outcome Measure

No significant change in UE function over 24 months after initiation of Ocrevus™ measured objectively by measure of time to completion (seconds) and functional

scores on TEMPA (0 to -3). The hypothesis is that there is (stabilization) no significant change (within 20%) of TEMPA score from baseline to 24 months

3.3.2 Secondary Outcome Measures

No significant change in UEFI, or 9HPT from baseline to 24 months. Exploratory measures: correlations between change in TEMPA/UEFI/9HPT scores and FSS, MUSIQOL and SDMT values from baseline through 24months after treatment initiation with Ocrevus™.

3.4 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study for any new adverse events (AEs), especially for those that may interfere with the testing or commercial dosing schedule.

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

This is a 24-month, prospective, observational study which will be conducted at the University of South Florida (USF) MS Center. On average 80-100 patients a week are seen at the study site. This large patient population offers a suitable number of potential candidates in order to meet the enrollment goal. This study will be conducted in adult multiple sclerosis patients who have upper extremity impairment and must satisfy the approved therapeutic indication for Ocrevus™. Decision to treat with Ocrevus™ must precede enrollment. We anticipate enrollment will be random and open to any patient that meets the criteria below which will aid in the evaluation of our results to the general MS population. The targeted population are those patients that more often rely on their upper extremity function for activities of daily living due to impairment in other systems such as gait.)

Every effort to maintain consistency (by use of the same rater) for the administration of the upper extremity assessments will be made. The same instructions for the patient questionnaires will be given at each time point.

4.1 SUBJECTS

4.1.1 Subject Selection

4.1.2 Inclusion Criteria

To be eligible for entry into this study, candidates must meet all of the following eligibility criteria at the time of study entry:

- Must give written informed consent and any authorizations required by local law (e.g., Protected Health Information [PHI])
- Aged 18-70 at the time of informed consent
- Must have a relapsing or progressive form of MS
- Male subjects and female subjects of child-bearing potential (including female subjects who are not post-menopausal for at least 1 year) must be willing to practice effective contraception (as defined by the investigator) during the study and be willing and able to continue contraception for 6 months after their last dose of study treatment
- EDSS 4.0-8.0
- UE weakness in at least one limb, defined as grade 4/5 in ≥ 2 muscles per limb
- Muscle weakness must be primarily related to MS
- Joint ROM must be within functional limits
- Patient must be able to perform 9HPT and TEMPA tests with at least one limb

4.1.3 Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of study entry:

- Severe weakness in bilateral upper limbs causing complete loss of function
- History of severe allergic or anaphylactic reactions or known drug hypersensitivity
- Female subjects considering becoming pregnant while in the study
- Female subjects who are currently pregnant or breast-feeding
- Unwillingness or inability to comply with the requirements of the protocol including the presence of any conditional (physical, mental or social) that is likely to affect the subject's ability to comply with the protocol.
- Active HBV infections
- Prior treatment with Ocrevus™
- Severe tremor/ataxia of the UE as defined by an EDSS with Cerebellar Functional System score of 3 or more due to upper extremity score (moderate tremor or clumsy movements interfere with function in all spheres)

- Severe spasticity of the UE as defined by EDSS, Pyramidal Functional System score- Upper Limb spasticity subscore of 3 or more (severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible)
- Cognitive impairment that may interfere with the conduct of the necessary testing (determined by the investigator)
- Any other reason that, in opinion of the Investigator and/or the Sponsor, the subject is determined to be unsuitable for enrollment in this study

4.2 METHOD OF TREATMENT ASSIGNMENT

There is no randomization in this study. Stratification of results by age and baseline UE strength may occur in the analysis.

4.3. STUDY TREATMENT

Ocrelizumab will be provided commercially to patients that participate in this study.

4.4 CONCOMITANT AND EXCLUDED THERAPY

Physical therapy will be documented and any other ongoing medications.

4.5 STUDY ASSESSMENTS

4.5.1 Overview of Study Visits

Screening/Baseline Visit (Day 0)

After the ICF is signed, the following information/assessments will be conducted:

- Review of medical history
- Review of inclusion/exclusion criteria
- Documentation on concomitant medications
- Demographic information
- Vital signs
- Measurement of UE function (TEMPA, 9HPT)
- Questionnaires (UEFI, FSS, SDMT, MUSIQOL)
- Physical examination/EDSS

Quarterly Visits* (Months 3, 9, 15, 21)

- Changes in concomitant medications and AE
- Questionnaires (UEFI, FSS, SDMT, MUSIQOL)
- Vital signs
- Interval history

*In the case of financial or physical limitations with the patient, the quarterly visits will be conducted via phone. In these instances, vital signs will not be obtained, as this will not affect the standard of care.

Semi-annual visits (before Ocrevus™ infusion) (Months 6, 12, 18)

- Changes in concomitant medications and AEs
- Review of concomitant medication and AEs
- Questionnaires (UEFI, FSS, SDMT, MUSIQOL)
- Physical examination/EDSS
- Vital signs
- Interval history
- Measurement of UE function (TEMPA, 9HPT)

Month 24 End of study (EOS)/Early discontinuation visit

In the event Ocrevus™ is discontinued prior to the end of the 24-month study, the patient will be asked to come in for EOS procedures. Any AEs attributed to Ocrevus™ in the opinion of the investigator, will be followed until resolved, and documented in the patient study chart.

- Review of concomitant medication and AEs
- Patient questionnaires (UEFI, FSS, SDMT, MUSIQOL)
- Physical examination/EDSS
- Vital signs
- Interval history
- Measurement of UE function (TEMPA, 9HPT)

4.6 DISCONTINUATION OF COMMERCIAL THERAPY

In the event Ocrevus™ is discontinued prior to the end of the 24-month study, the patient will be asked to come in for EOS procedures. Any AEs attributed to Ocrevus™ in the opinion of the investigator, will be followed until resolved, and documented in the patient study chart.

4.7 SUBJECT DISCONTINUATION

If a patient discontinues use of Ocrevus, for any reason, they will be asked to attend an EOS visit to conduct final assessments (same format as month 24 visit).

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 AEs 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

All protocol violations will be accounted for and summarized in the results and discussion. If there are large amounts of missing data imputation measures may be used.

Demographic information will be collected on all patients in order to present descriptive statistics of the population.

4.9.2 Analysis of Treatment Group Comparability

There is only one designated treatment group. Descriptive statistics of the baseline characteristics of the enrolled population will be presented in the final report and manuscript.

4.9.3 Efficacy Analysis

a. Primary Endpoint

1. TEMPA scores after 24 months of Ocrevus™ treatment.
Paired sample t-test to compare the 24 month measurements to the baseline measurements.

Mean within-patient changes from baseline through 24 months (TEMPA). One-way repeated measures ANCOVA for TEMPA scores from baseline, 6 months, 12 months, 18 months, 24 months which will account for baseline characteristics (baseline disability level). A soft stratification will be applied so that recruitment will aim to include a spread of types of patients, those below overall EDSS of 6.0 and those above 6.0. If more than 2/3 of total enrollment is in one of the categories, the study team will reestablish efforts to recruit for the other cohort.

If data does not have normal distribution, then other non-parametric analysis will be employed (such as sign test for TEMPA functional score).

The threshold to determine a significant clinical change will be >20% from baseline value. This clinically significant difference is estimated based on data from the Oratorio trials that showed progression among both groups (placebo and Ocrevus™) but to a lesser extent in the Ocrevus™ arm with an established clinically significant threshold of 20%(data will be requested from sponsor for use to review 9HPT results for the abnormal function at baseline group of patients). Measures will be collected and analyzed as units of time (seconds) and as functional scores on an ordinal scale that range from 0 to -3 (0 indicating

no signs of dysfunction).Ad hoc analysis may occur that includes evaluation of patients with significant clinical changes versus those that did not have significant clinical change based on any of the subscales within the TEMPA or physical exam. We will review >15%, >20% and >25% [in better hand and in worse hand] change from baseline with increases in time implying clinical progression and stability or decrease in time implying stability or improvement in function

b. Secondary Endpoints

Pearson correlation coefficients will be calculated to evaluate correlations between UE function (measured by TEMPA and 9HPT) primarily at baseline but also at each time point over the 24-month time period to compare patient responses on the UEFI, FSS, and MUSIQOL. Correlations with the primary endpoint scores and the SDMT will also be analyzed for any indication of new cognitive impairment that may interfere with the interpretation of the results.

4.9.4 Safety Analysis

No safety analysis will occur as these patients will be receiving commercial Ocrevus. A summary of adverse events will be constructed using descriptive statistics.

4.9.5 Missing Data

Study staff will work to ensure missing data is minimized. If there are less than two percent of time points missing, then during analysis, last value carry forward imputation will be used. If greater than two percent missing, multiple point imputation measures will be used.

4.9.6 Determination of Sample Size

It is expected that 30 patients will be eligible to enter this study during the proposed timeframe. This is a pilot study; the TEMPA is a more comprehensive assessment of upper extremity function which we will use in the analysis of this group of patients to evaluate what percentage remain stable (within 20% variation from baseline) and analyze correlations with other measures of upper extremity function (9HPT and patient perception using the UEFI). Therefore, this is not a calculated sample size as there is a lack of historical data available for this population and the modalities of testing we plan to utilize. We do not have historical data to gather estimates for an accurate power calculation. We plan to gather data on 30 patients but will screen up to 35 in case of screen failures or early withdrawals. Even with the limited calculations we believe that we will be able to analyze for a clinically meaningful lack of change (stabilization).

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) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), 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).
- 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 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 as described in section 5.1 where the subject has been exposed to a Genentech product must be reported. The Reporting period begins after informed consent is obtained and initiation of any study procedures and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through 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 ocrelizumab (see following guidance), and actions taken.

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

Yes

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

No

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

Expected AEs are those AEs that are listed or characterized in the Package Insert (P.I.)or current Investigator Brochure (IB).

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

Unexpected disease progression defined by increase in 1 point on the upper extremity strength scores in the Pyramidal FSS of the EDSS above baseline subsequently confirmed at repeat assessment 6 months later would imply worsening of upper extremity function and require clinical evaluation.

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 time points should be adopted. Examples of non-directive questions include:

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

Specific Instructions for Recording Adverse Events

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

a. Diagnosis vs. Signs and Symptoms

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

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 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 Update current versions) 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 ocrelizumab or within 6 months 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).

g. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior ocrelizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE adequately to Genentech Drug Safety during the 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 (AESI)

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

to other parties (e.g., Regulatory Authorities) may also be warranted.

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

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

j. Adverse Event Reporting

The Sponsor will track all protocol-defined AE and pregnancy reports originating from the Study for the Product.

Investigators must report all AEs, SAEs, AESIs pregnancy reports and special situation reports (if applicable) adequately to Genentech within the timelines described below. The completed Medwatch or CIOMS I form or Genentech approved reporting forms should be faxed 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 sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

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.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

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/Roche within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AEs that are unrelated to the Product shall be reported to Genentech/Roche via the AE master log at least annually.

- **AESIs**
  AESIs shall be forwarded to Genentech/Roche within fifteen (15) calendar days of the awareness date.

- **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.

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 (Section C & D), the report should include the following information within the Event Description (section B.5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the AE 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 AE 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

5.5 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Sponsor 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 filed a clinical trial approval, in compliance with local regulations.

Genentech will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM). The

Sponsor will be responsible for the distribution of safety information to its own investigators, where relevant.

5.6 Additional Reporting Requirements for IND Holders

For Investigator-Initiated 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 AE that is unexpected and assessed by the Investigator to be possibly related to the use of ocrelizumab. An unexpected AE is one that is not already described in the ocrelizumab IB. 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 AE is one that is not already described in the ocrelizumab IB.

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:

University of South Florida IRB
12901 Bruce B. Downs Blvd, MDC35
Tampa, FL 33612-4799
rsch-arc@usf.edu

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: ocrelizumab-iis-d@gene.com and ctvist_drugsafety@gene.com

Other Reports

The sponsor will forward a copy of the Final Study Report or publication 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, to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com and your Genentech MSL.

QUERIES

Queries related to the Study will be answered by University of South Florida. 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. University of South Florida agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

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

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

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 AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs 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 AE 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

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of the subject to the applicable regional or national regulations and principles of confidentiality for each participating center. Information contained therein will be maintained in accordance with applicable law protecting patient privacy; including the provisions of 45 CFR Part 164 promulgated under the Health Insurance Portability and Accountability Act (HIPPA) in addition to applicable regional, national, or provincial regulations, and may be inspected by the Investigator, the investigators staff. Processing, evaluation, or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional.

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. All data will be entered into a computer that is password protected. Data will be stored in a locked office of the investigators and maintained for a minimum of three years after completion of the study. When any data are published all identifiers will be removed. When data or resources are shared with other study investigators or collaborators no personal identifiers will be shared.

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.

The results of this study will be submitted for poster presentation at an annual conference in the year that the data has been analyzed (CMSC or ACTRIMS). The manuscript will be submitted for publication after poster presentation to the International Journal of Multiple Sclerosis Care.

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 A Schedule of Assessments

	Screening/ BL[1,2]	M3	M6[3]	M9	M12[3]	M15	M18[3]	M21	M24[3]
Informed Consent	X								
Review of Medical History	X								
Review of inclusion/exclusion	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Demographics	X								
Patient Questionnnaires (UEFI, SDMT, FSS, MUSIQOL)	X	X	X	X	X	X	X	X	X
Physical Exam (and EDSS)	X		X		X		X		X
Vital Signs	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X
Interval History	X	X	X	X	X	X	X	X	X
Review AEs	X	X	X	X	X	X	X	X	X
Measurement of UE function (TEMPA, 9HPT, Jamar dynamometer)	X		X		X		X		X
Relapse Assessment[5]	X	X	X	X	X	X	X	X	X

1. The baseline visit will occur within 4 weeks of the screening visit.
2. Acceptable windows for all visits are +/- 14 days. In rare cases where the first infusion is greater than 2 months from the baseline visit, the month 3 visit and subsequent visits will be calculated based on the initial infusion date.
3. Semiannual visits will occur prior to the next scheduled Ocrevus™ infusion
4. Vitals signs will be collected for subjects who conduct the quarterly visit at clinic. Vital signs will not be collected at quarterly visits conducted via phone.
5. If relapse is suspected, this will be captured as an AE and treated at the discretion of the investigator. Documentation will include any suspicion for PML

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

Appendix C UEFI

Today, *do you* or *would you* have any difficulty at all with:

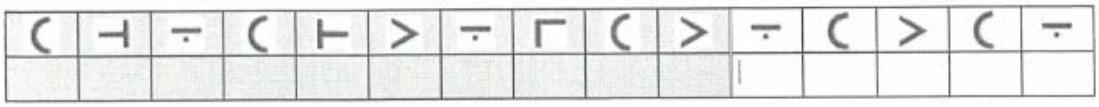
	Activities	Extreme difficulty or unable to perform activity	Quite a bit of difficulty	Moderate difficulty	A little bit of difficulty	No difficulty
1	Any of your usual work, housework, or school activities	0	1	2	3	4
2	Your usual hobbies, recreational or sporting activities	0	1	2	3	4
3	Lifting a bag of groceries to waist level	0	1	2	3	4
4	Lifting a bag of groceries above your head	0	1	2	3	4
5	Grooming your hair	0	1	2	3	4
6	Pushing up on your hands (eg, from bathtub or chair)	0	1	2	3	4
7	Preparing food (eg, peeling, cutting)	0	1	2	3	4
8	Driving	0	1	2	3	4
9	Vacuuming, sweeping or raking	0	1	2	3	4
10	Dressing	0	1	2	3	4
11	Doing up buttons	0	1	2	3	4
12	Using tools or appliances	0	1	2	3	4
13	Opening doors	0	1	2	3	4
14	Cleaning	0	1	2	3	4
15	Tying or lacing shoes	0	1	2	3	4
16	Sleeping	0	1	2	3	4
17	Laundering clothes (eg, washing, ironing, folding)	0	1	2	3	4
18	Opening a jar	0	1	2	3	4
19	Throwing a ball	0	1	2	3	4
20	Carrying a small suitcase with your affected limb	0	1	2	3	4
	Column totals					

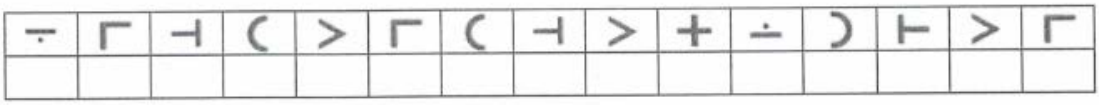
Minimum level of detectable change (90% confidence): 9 points **SCORE: ____ / 80**

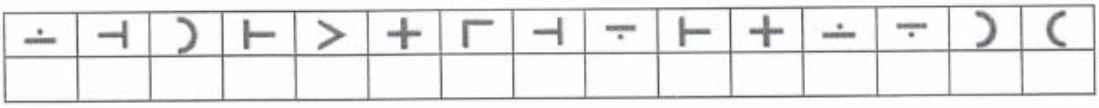
Page 2

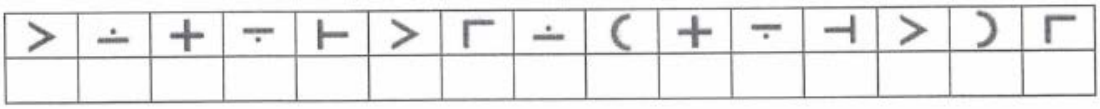
Appendix D
SDMT

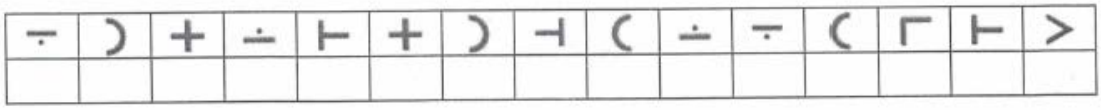
KEY

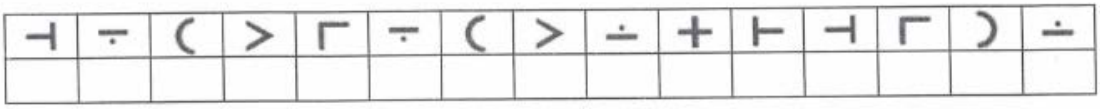












Appendix E
Jamar handheld dynamometer

Appendix F
9-hole peg test

UPPER EXTREMITY FUNCTION: NINE-HOLE PEG TEST (9-HPT)

Subject ID Number | Subject Initials | Visit Date: Day Month Year

9-HOLE PEG TEST

DOMINANT HAND *(Check one):* Right ☐ Left ☐

DOMINANT HAND

Trial 1

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify: _____

☐ Other ➡ _____

Trial 2

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify: _____

☐ Other ➡ _____

Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No
If Yes, please specify reason(s) for more than two attempted trials:

NON-DOMINANT HAND

Trial 1

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify: _____

☐ Other ➡ _____

Trial 2

☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

_____

_____

If trial was not completed *(mark one):*

☐ Unable to complete trial due to physical limitations ➡ Specify: _____

☐ Other ➡ _____

Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No
If Yes, please specify reason(s) for more than two attempted trials:

Appendix G
Fatigue Severity Scale (FSS)

fatigue severity scale (fss)

Please circle a number to the right of each of these following nine statements to indicate how much you agree with the statement. *"1"* represents *"strongly disagree"*, *"4"* represents *"neither disagree nor agree"*, while *"7"* represents *"strongly agree"*.

1.	my motivation is lower when I am fatigued	*1*	*2*	*3*	*4*	*5*	*6*	*7*
2.	exercise brings on my fatigue	*1*	*2*	*3*	*4*	*5*	*6*	*7*
3.	I am easily fatigued	*1*	*2*	*3*	*4*	*5*	*6*	*7*
4.	fatigue interferes with my physical functioning	*1*	*2*	*3*	*4*	*5*	*6*	*7*
5.	fatigue causes frequent problems for me	*1*	*2*	*3*	*4*	*5*	*6*	*7*
6.	my fatigue prevents sustained physical functioning	*1*	*2*	*3*	*4*	*5*	*6*	*7*
7.	fatigue interferes with carrying out certain duties and responsibilities	*1*	*2*	*3*	*4*	*5*	*6*	*7*
8.	fatigue is among my three most disabling symptoms	*1*	*2*	*3*	*4*	*5*	*6*	*7*
9.	fatigue interferes with my work, family, or social life	*1*	*2*	*3*	*4*	*5*	*6*	*7*

The average score per question for a group of healthy adults was found to be 2.3, so a total for the scale of 20.7.

Krupp L B et al. *The Fatigue Severity Scale.* Arch Neurol 1989; 46: 1121-1123.

Appendix H MUSIQoL

Due to your MS, during the past 4 weeks, have you… *For each question, check the response that is closest to your feelings*	Never Not at all	Rarely A little	Sometimes Somewhat	Often A lot	Always Very much
13 been troubled by loss of memory?	☐	☐	☐	☐	☐
14 had difficulty concentrating: i.e. when reading, watching a film, following a discussion…?	☐	☐	☐	☐	☐
15 been troubled by your vision: worsened or unpleasant?	☐	☐	☐	☐	☐
16 experienced unpleasant feelings: i.e. hot, cold…?	☐	☐	☐	☐	☐
17 talked with your friends?	☐	☐	☐	☐	☐
18 felt understood by your friends?	☐	☐	☐	☐	☐
19 felt encouraged by your friends?	☐	☐	☐	☐	☐
20 talked with your spouse/partner or your family?	☐	☐	☐	☐	☐
21 felt understood by your spouse/partner or your family?	☐	☐	☐	☐	☐
22 felt encouraged by your spouse/partner or your family?	☐	☐	☐	☐	☐

Due to your MS, during the past 4 weeks, have you… *For each question, check the response that is closest to your feelings*	Never Not at all	Rarely A little	Sometimes Somewhat	Often A lot	Always Very much
23 felt satisfied with your love life?	☐	☐	☐	☐	☐
24 felt satisfied with your sex life?	☐	☐	☐	☐	☐
25 felt that your situation is unfair?	☐	☐	☐	☐	☐
26 felt bitter?	☐	☐	☐	☐	☐
27 been upset by the stares of other people?	☐	☐	☐	☐	☐
28 been embarrassed when in public?	☐	☐	☐	☐	☐
29 been satisfied with the information on your disease or the treatment given by the doctors, nurses, psychologists… taking care of your MS?	☐	☐	☐	☐	☐
30 felt understood by the doctors, nurses, psychologists… taking care of your MS?	☐	☐	☐	☐	☐
31 been satisfied with your treatments?	☐	☐	☐	☐	☐