PROTOCOL

TITLE:	**A PHASE 4, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY OF OCRELIZUMAB IN PATIENTS WITH RADIOLOGICALLY ISOLATED SYNDROME**
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TEST PRODUCTS:	Ocrelizumab (RO4964913) (OCREVUS®)
INDICATION:	Prevention of clinical multiple sclerosis in individuals with radiologically isolated disease.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
β-hCG	beta subunit human chorionic gonadotropin
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
CSF	cerebrospinal fluid
DIS	dissemination in space
DMT	disease-modifying therapy
DSS	disease status scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
Gd	gadolinium
FS	Functional Systems
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HepCAb	hepatitis C antibody
IFN-β	interferon beta
Ig	immunoglobulin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice/web response system
LLN	lower limit of normal
LPLV	last patient, last visit
LP	lumbar puncture
MMRM	mixed model with repeated measure
MRI	magnetic resonance image
MS	multiple sclerosis
NfL	neurofilament light (chain)
OCB	oligoclonal bands
PCR	polymerase chain reaction
PML	progressive multifocal leukoencephalopathy

PPMS	primary progressive multiple sclerosis
PRO	patient reported outcome
RIS	radiologically isolated syndrome
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
scRNAseq	single-cell RNA sequencing
SPMS	secondary progressive multiple sclerosis

BACKGROUND

BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and degenerative disease of the CNS that affects approximately 2.3 million people worldwide (Tullman et al. 2013 MSIF 2013). While MS is a global disease, its prevalence is highest in North America and Europe (140 and 108 per 100,000 people, respectively) (MSIF 2013). A recent study by leading experts, launched and supported by the National MS Society, estimates that in 2017 nearly 1 million adults (up to 913,925) were living with MS in the United States. This is more than twice the previously reported estimates (Wallin et al. 2019). MS primarily affects young adults, with nearly 80% of patients having an age of onset (i.e. initial clinical presentation to a physician) between 20 and 40 years (Tullman 2013). Overall, there is a strong gender bias: MS is approximately twice as prevalent in women as in men, except in individuals with the primary-progressive form of the disease, where there is no gender prevalence difference (MSIF 2013; Tullman 2013). Reasons for these observed differences are unclear. However, once progression begins, it continues at similar rates in women and men (Leray et al. 2010).

MS can be subcategorized into three major phenotypic disease patterns, including relapsing-remitting MS (RRMS), primary-progressive MS (PPMS) and secondary progressive MS (SPMS). In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (i.e., RRMS). Over time, and if left untreated, the majority of these patients transition to a secondary-progressive form characterized by worsening neurologic disability, either with or without occasional super-imposed relapses (i.e., active- or non-active SPMS, respectively). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual often insidious disease progression (Tullman 2013). The term ‘relapsing multiple sclerosis (RMS)’ applies to those patients with either RRMS or SPMS who continue to suffer relapses (i.e. active-SPMS). Nonetheless, overwhelming evidence suggests that neuroinflammation is present throughout all clinical courses of MS (Frischer et al. 2009). Differences between disease phenotypes may be due to the differential contribution of inflammatory and neurodegenerative processes to the pathology of CNS damage over time (Frischer et al. 2009, 2015). Therefore, patients with MS regardless of subtype and stage, share a common underlying inflammatory pathophysiology that therefore constitutes a common therapeutic target.

Although the exact etiology of MS remains largely unknown, there is consensus that MS is an autoimmune disease driven by aberrant functioning of both the adaptive and innate immune system in genetically susceptible individuals. Considerable evidence suggests that early intervention with disease modifying therapies (DMT) is beneficial for MS

patients and is associated with more favorable long-term outcomes. Significant advances have been made in the identification of biomarkers and risk-factors that lead to earlier and thus more accurate diagnosis of MS. Magnetic resonance imaging (MRI) is among one of the most valuable biomarkers for MS diagnosis. An unintended consequence of widespread use of MRI by the medical community has been incidental findings of CNS abnormalities that are consistent with inflammatory or demyelinating lesions. This has augmented the overall awareness of MRI findings suggestive of MS, particularly in individuals who are otherwise asymptomatic and clinically "normal," but are nevertheless at increased risk of developing clinical CNS demyelinating disease.

BACKGROUND ON RADIOLOGICALLY ISOLATED SYNDROME

The term 'radiologically isolated syndrome' (RIS) was first introduced in 2009 by Okuda and colleagues to describe the presence of these incidentally identified CNS white matter anomalies that were typical of inflammatory demyelinating disease in subjects with no present or past symptoms suggestive of MS (Okuda et al. 2009). The diagnostic criteria for RIS proposed by Okuda et al. requires a heavy lesion burden, strictly defining the morphology, size, location, number, and distribution of lesions fulfilling at least three out of four Barkhoff criteria for dissemination in space (DIS) in order to differentiate those at highest-risk for developing MS (Table 1). In addition, the Okuda criteria also include an indication for MRI other than suspected MS, and exclude other disease entities that could better account for the observed paraclinical anomalies. Approximately one-third of patients with RIS will experience a first acute or progressive clinical event related to CNS demyelination within 5 years, while two-thirds of patients with RIS show radiologic progression with a median of 2.7 years (Lebrun et al. 2008; Granberg et al 2013; Okuda et al. 2014, and Yamout 2017). Several factors have been associated with conversion to MS in RIS patients, including younger age (<40), sex (male) and the presence of spinal cord or infratentorial brain lesions (Okuda et al. 2011; Etemadifar et al. 2014; Okuda et al. 2014; Makhani 2017;Thouvenot et al. 2019). Abnormal cerebrospinal fluid (CSF) findings, including the presence of oligoclonal bands (OCBs) and/or elevated IgG index, have also been suggested as potential risk factors for clinical conversion (Nakamura et al. 2014; Gastaldi 2017; Matute-Blanch et al. 2018; and Makhani et al. 2019).

Table 1 Diagnostic Criteria for Dissemination in Space

Okuda Diagnostic Criteria for RIS	2017 McDonald Diagnostic Criteria for MS
The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:	≥1 T2-hyperintense lesions characteristic of MS in ≥2 of 4 CNS areas Periventricular Cortical or juxtacortical Infratentorial brain regions

Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum T2 hyperintensities measuring >3mm and fulfilling ≥3 of 4 Barkhof criteria for DIS ≥9 lesions or ≥1 Gd+ lesion ≥3 periventricular lesions ≥1 juxtacortical lesion ≥1 infratentorial lesion	Spinal cord

CNS=central nervous system; Gd=gadolinium; MRI=magnetic resonance imaging; MS=multiple sclerosis; RIS=radiologically isolated syndrome

Pathological changes and degenerative processes occur very early in MS, even years before clinical signs surface. In this regard, studies have demonstrated a close association between RIS and MS since the initial formal description in 2009. Therefore, it has been suggested that RIS represents a preclinical phase of MS (Siva et al. 2009; Amato et al. 2012; and Boyko 2019). Similar lesion loads and brain atrophy have been demonstrated in RIS and patients with well-established MS (De Stefano et al. 2011; Amato et al. 2012). Patients with RIS have subclinical cognitive impairment (Hakiki et al. 2008; Lebrun et al. 2010; Amato et al. 2012; Cortese et al. 2016; and Labiano-Fontcuberta et al. 2016), inflammation (Lebrun 2009; Rossi et al. 2015; and Bjornevik et al. 2019) and CNS pathology (Stromillo et al. 2013) similar to that described in patients with MS. Furthermore, other non-descript neurologic symptoms that do not yet surpass the clinical threshold often present in patients at high-risk for developing MS (e.g., anxiety, depression, migraine, lower cognitive performance, etc.). It is widely recognized that this early preclinical and prodromal phase of disease may go unnoticed for many years prior to the clinical manifestation of MS (Cortese et al. 2016; Wijnands et al. 2017; Disanto 2018; Bjornevik et al. 2019, Wijnands et al. 2019; Zhao et al. 2020). This is accompanied by increased health care utilization in the years preceding MS diagnosis (Wijnands et al. 2017; Disanto et al. 2018; Wijnands et al. 2019a; Wijannds et al 2019b). Serum neurofilament light chain (NfL), a biomarker of neuroaxonal injury, has been found to be elevated years before the clinical onset of MS (Bjornevik et al. 2019), further indicating not only that a preclinical and prodromal phase of MS exists, but also that subclinical tissue damage is already occurring during this early stage of disease.

While Okuda criteria have now been widely used to study RIS, they require a higher burden of radiologic disease than modern diagnostic criteria for MS. The 2017 McDonald criteria are used in clinical practice to identify MS. This iteration of the McDonald criteria

has allowed earlier identification of MS, requiring as few as two CNS lesions among patients presenting with a first clinical symptom of disease (Thompson et al. 2018).

BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre–B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Based on the results of ocrelizumab Phase III studies in patient populations with relapsing MS (RMS) and PPMS, ocrelizumab was approved by the US Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS and by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Two identical randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events was similar in patients treated with ocrelizumab compared with interferon β-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]).

Refer to the Ocrelizumab Investigator's Brochure and/or local prescribing information for details on nonclinical and clinical studies of ocrelizumab.

STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study is designed to investigate the treatment effect of ocrelizumab compared with placebo on clinical and radiological outcomes in patients with RIS (i.e., asymptomatic CNS lesions fulfilling the 2017 McDonald criteria for DIS), as well as neuroimaging, serologic, immunologic and other exploratory biomarkers of MS disease biology in order to improve the understanding of B cell biology in early disease pathophysiology, characterize the emergence of CNS autoimmunity, and the mechanism of action of ocrelizumab in this population.

In general, DMTs have been demonstrated to be more effective when utilized at the onset of disease (Comi et al. 2001 and 2009; Leist et al. 2014; Miller 2014). Multiple randomized clinical studies have supported the benefit of treatment early in the course of disease, demonstrating that early initiation of DMT after a first event in patients with CIS significantly delays the time to a second clinical attack and reduces the accumulation of new MRI lesions (Comi et al. 2001 and 2009; Goodin 2009; Leist et al. 2014; Miller 2014). Yet despite this evidence supporting the benefit of early DMT use, it is reported that most clinicians adopt a “wait-and-watch” approach for RIS, periodically monitoring patients and delaying treatment until the emergence of clinical symptoms (Sellner et al. 2010; Alshamrani 2017). Delaying treatment in at-risk RIS patients could result in irreversible CNS damage and permanent disability, even despite repair and compensatory mechanisms that might account for the lack of obvious clinical symptoms (Akbar et al. 2016; Labiano-Fontcuberta 2017; Okuda 2017; and Makhani et al. 2018). Furthermore, it has been reported that subjects with RIS evolve to PPMS with a similar frequency as that observed in the general MS population, providing further evidence that RIS represents a preclinical stage of disease that is biologically part of the MS spectrum (McDonnel et al. 2003; Kantarci et al. 2016). In this regard, patients with RIS have been demonstrated to have evidence of early axonal loss (Stromillo et al. 2012, 2013; Azevedo et al. 2015), brain atrophy (De Stefano et al. 2011, Labiano-Fontcuberta et al. 2016a; Labiano-Fontcuberta et al. 2016b; Alcaide-Leon et al. 2018), and subclinical inflammatory disease, including elevated serum NfL (Bonzano et al. 2013; Disanto et al. 2016; Knier et al. 2016; Malute-Blanch et al. 2018), and IL-8 (Rossi et al. 2015), as well as retinal nerve fiber layer thinning (Vural et al. 2020) as observed by OCT. Cognitive deficits, such as impaired information processing speed (Achiron et al; 2003; Lebrun et al. 2010; Amato et al. 2012; D’Anna et al. 2014; Labiano-Fontcuberta et al. 2016; Menascu et al. 2019), and increased anxiety and depression have also been noted in patients with RIS (Labiano-Fontcuberta et al. 2015). These changes, often subtle, may be missed during routine neurological assessments and can significantly impact quality of life even if physical functioning remains intact (Glanz et al. 2010).

Despite a pathophysiologic rationale for treatment, limited data exist on the use of DMT in RIS. Randomized, clinical trials are needed to provide evidence for the benefit: risk of

intervening therapeutically at this stage of disease (Okuda et al. 2015; Lebrun et al. 2016). The results of the first randomized clinical trial in RIS have recently been relased: ongoing use of the MS medication dimethyl fumarate reduced the chances of RIS patients converting to clinical MS (Okuda et al. 2022). No changes to the drug's label have been made, however, and dimethyl fumarate will require continuous use for ongoing efficacy. It is not clear that a lifelong immunotherapy will be an acceptable method for treating RIS. Early intervention in the RIS population with short-term use of ocrelizumab, a high efficacy DMT, provides the unique opportunity to address this unmet need.

The Phase III program of ocrelizumab comprised three pivotal Phase III studies that evaluated ocrelizumab 600 mg administered as an IV infusion at a fixed-interval schedule every 24 weeks, which demonstrated favorable benefit-risk profile in RMS and PPMS. Together, these data derived from a total of 2381 patients demonstrated that selective depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including relapse rate, MRI outcomes and disability progression.

Data from the ocrelizumab development program support the hypothesis that B cells are central to the pathogenesis of MS. B cells play a significant role in the pathophysiology of MS at all stages of disease (Hauser et al. 2017; Montalban et al. 2017; Sabatino 2019; Lassmann 2019). B cells are involved in cytokine regulation and antigen presentation to T cells, myeloid cell activation, and are also the source of intrathecal antibody production, including clonally expanded IgG bands (oligoclonal bands [OCB]) detected in the CSF of approximately 90% of MS patients (Dobson et al. 2013; Li 2018). Ectopic lymphoid follicles rich with B cell aggregates can be found in the meninges of MS patients and are associated with cortical demyelination and neuroaxonal damage (Magliozzi et al. 2007 and 2010; Howell et al. 2011). Recent studies investigating the role of B cells in the early stages of MS (i.e., CIS) have revealed that markers of B cell activation and antigen-driven responses within the CSF predict conversion to clinically definite MS and correlate with MRI activity, onset of relapses and future disability progression (Serafini et al. 2004; Imrell et al. 2009; Joseph et al. 2009; Sellebjerg et al. 2009; Brettschneider et al. 2010; Magliozzi et al. 2010; Howell et al. 2011; Kalinowska-Łyszczarz et al. 2011; Khademi et al. 2011; Disanto et al. 2012; Dobson et al. 2013). Furthermore, in RIS it has been observed that B cells are skewed toward a proinflammatory phenotype and produce less of the immunoregulatory cytokine IL-10. This was associated with the emergence of disease activity and poor prognosis (Guerrier et al. 2018). These data along with the profound clinical benefit of ocrelizumab on suppressing disease activity and disability progression in RMS and PPMS, underscore the central role of B cells in the immunopathophysiology of MS.

Given the remarkable success of ocrelizumab on clinical outcomes in MS, the question arises as to whether treatment in radiologically isolated disease might provide an even

more favorable therapeutic benefit than in patients with established disease. Early intervention in this population with ocrelizumab, a high efficacy DMT, provides the unique opportunity to address this unmet need. Ocrelizumab is particularly attractive for use in RIS patients at high-risk for developing MS because of (1) its well-characterized safety profile, (2) administration and dosing schedule, and (3) that it targets peripheral B cells that eventually migrate into the CNS and drive compartmentalized CNS inflammation (i.e., CNS leukocyte recruitment, focal demyelinated lesions, intrathecal antibody production with OCBs, etc.). The B cell profile that reconstitutes after anti-CD20 depletion exhibits a naïve phenotype that produce high levels of IL-10 (Duddy et al. 2007; Bar-Or et al. 2010; Barr et al. 2012; Li et al. 2015; Longbrake 2016; Li 2018) and less proinflammatory cytokines (i.e., IL-6, TNF, GM-CSF, and LT). This suggests that B cell depletion may alter immunoregulatory networks and restore the proinflammatory to anti-inflammatory imbalance that contributes to long lasting impact on MS disease activity and disability progression. Whether therapeutic intervention with ocrelizumab during RIS "functionally-resets" the immune system and thereby leads to durable improvement of long-term outcomes and the delay or prevention of the clinical manifestation of MS is unknown.

Administering three courses of ocrelizumab permits the interrogation of the immunodynamics surrounding the emergence of CNS autoimmunity and the reconstitution of the immune system following anti-CD20 B cell depletion. Understanding the effect of B cell depletion in RIS will provide invaluable insight into MS pathogenesis as well as the mechanism of action of ocrelizumab, both of which remain poorly understood.

While this study is the first clinical trial investigating the use of ocrelizumab in patients with RIS, ocrelizumab is well established as a standard of care, high efficacy disease-modifying therapy for the treatment of patients with RMS (including CIS, RRMS, SPMS) and PPMS; with a favorable safety profile in over 130,000 patients worldwide since its US FDA approval in 2017. Therefore, the benefits versus the risks for individual participants treated with ocrelizumab for study-related procedures are considered acceptable.

OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVE(S)

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the treatment effect of ocrelizumab compared with placebo on delaying the time to development of new radiologic or clinical evidence of MS.

Primary Efficacy Endpoint:

Time to development of first new radiologic (e.g., new or enlarging T2 lesions, T1 gadolinium-enhancing lesions consistent with MS) or clinical evidence of MS (i.e., neurological event resulting from CNS demyelination, as evidenced by acute or progressive clinical syndrome consistent with MS).

A detailed description of the primary endpoints and estimands are provided in Section 6.4.1.

SECONDARY OBJECTIVE(S)

Secondary Efficacy Objective

The secondary objectives for this study are to understand the treatment effect of ocrelizumab compared with placebo on clinical, neuroimaging and serum neurofilament light (NfL) biomarkers that are associated with disease activity, and with the clinical response to ocrelizumab.

Secondary Efficacy Endpoints:

Cumulative number of new or enlarging T2 lesions identified at Weeks 48, 104 and 208

Change in T2-lesion volume from Baseline to Weeks 48, 104 and 208

Cumulative number of new T1 gadolinium-enhancing lesions identified at Weeks 48, 104 and 208

Change from Baseline to Weeks 48, 104 and 208 in total brain volume

Change from Baseline to Weeks 48, 104 and 208 in total spinal cord volume

Change from Baseline to Weeks 48, 104 and 208 in serum NfL (sNfL)

Exploratory Efficacy Objectives

The exploratory objectives for this study are to evaluate inflammatory, neurodegenerative, and exploratory biomarkers of disease activity in the blood and cerebrospinal fluid (CSF) and their correlations with radiologic, clinical and patient reported outcomes.

Exploratory Efficacy Endpoints:

Change from Baseline to Weeks 48, 104 and 208 in white matter volume, gray matter volume, and thalamic volume

Change from Baseline to Weeks 48, 104 and 208 in spinal cord white and gray matter volume

Change from Baseline to Week 104 and 208 in CSF immune cell populations frequency and phenotype

Change from Baseline to Week 104 and 208 in CSF NfL levels

Percent change in the presence of CSF oligoclonal bands (OCB) from Baseline to Weeks 104 and 208

Percent change in normalization of CSF IgG index from Baseline to Weeks 104 and 208

Change from Baseline to Weeks 104 and 208 in CSF biomarkers (i.e., CSF Weeks 104 and 208 only), including CXCL13, BAFF (B cell activating factor), TNF, IL-6, IL-10, IL-17, interferon-gamma, IL-4, IL-23, IL-8, soluble CD27 (sCD27), genetic risk factors (HLA-DRB1*15:01) or other emerging exploratory markers of disease biology as appropriate

Change from Baseline to Weeks 48, 104, and 208 in slowly evolving lesions (SEL)

Change from Baseline to Weeks 24, 48, 72, 104, 130, 156, 182 and 208 in peripheral blood immune cell population frequency and phenotype, including B cells, T cells and innate immune cells (monocyte, macrophage, neutrophils, natural killer cells, etc.)

Change from Baseline to Weeks 24, 48, 72, 104, 130, 156, 182 and 208 in peripheral blood biomarkers, including CXCL13, BAFF (B cell activating factor), TNF, IL-6, IL-10, IL-17, interferon-gamma, IL-4, IL-23, IL-8, soluble CD27 (sCD27), genetic risk factors (e.g., HLA-DRB1*15:01) or other emerging exploratory markers of disease biology as appropriate

Change from Baseline to Weeks 24, 48, 72, 104, 130, 156, 182 and 208 in patient reported outcomes, including quality of life, fatigue, depression, and disability, as measured by Neuro-QoL™

Change from Baseline to Weeks 24, 48, 72, 104, 130, 156, 182 and 208 in cognitive function and information processing speed as measured by symbol digit modality test (SDMT)

Correlation between changes in compartment-specific biomarkers of disease biology with radiologic and/or clinical disease outcomes

Correlation between changes in patient reported outcomes, including SDMT, and radiologic and/or clinical disease outcomes

Correlation between changes in compartment-specific immune cell subsets with radiologic and/or clinical disease outcomes.

Correlation between changes in NfL levels and radiologic and/or clinical disease outcomes

Correlation between changes in CSF abnormalities (OCB and IgG index) and radiologic and/or clinical disease outcomes

SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo on the basis of the following endpoints:

Nature, frequency, severity, and timing of adverse events

Vital signs, physical findings, and clinical laboratory results during and following study drug administration

Adverse events related to biomarker sample collection

STUDY DESIGN

DESCRIPTION OF THE STUDY

This study includes a main study for all patients enrolled and one optional sub-study: an Immune Cell Network sub-study. The following is a description of the main study. A schedule of activities (SOA) for the main study is provided in Appendix 1. For details on the Immune Cell Network sub-study, please refer to

Appendix 2. For the sub-study schema, please refer to **Appendix 3**

This is a multicenter, randomized, double-blind, placebo-controlled, Phase 4 study in which eligible patients with RIS (as defined by meeting 2017 McDonald criteria for DIS) will be randomized 1:1 to receive ocrelizumab treatment or placebo (standard of care). Three courses of ocrelizumab or placebo will be administered over the course of the study. The first course of ocrelizumab will be administered as two 300 mg infusions at Week 0 (Day 1) and Week 2 (Day 15), with the subsequent second- and third-courses given as a single 600 mg infusion at Weeks 24 and 48. Placebo will be administered at the same timepoints. Screening will occur over a 45-day period.

All participants must have had CSF analysis at baseline. For those who have had lumbar puncture and CSF analysis prior to screening for this study, historical results (for oligoclonal banding) will be accepted as long as original source documentation can be provided. Optional CSF (baseline, weeks 104 and 208, with paired blood) can still be contributed to the study. For those who have not had prior CSF analysis, lumbar puncture and CSF analysis will be required at baseline with two optional follow-up lumbar punctures post-baseline (Weeks 104 and 208). Refer to Figure 1 Study Schema.

The double-blind phase will be considered complete when the results of the primary analysis are disclosed and the study becomes unblinded to sites. If the projected number of radiological or clinical events (21) has not been reached when the last patient completes 4 years in the double-blind phase because of slower than anticipated event rates, the double-blind phase may be extended until the required number of events have occurred. After the primary analysis is complete, patients will remain in the study and be followed for a minimum total of 3 years after treatment.

As the primary analysis is event driven, the study duration in the double-blind phase will vary for each patient.

The study population will consist of patients with RIS, defined as individuals with magnetic resonance imaging (MRI) anomalies within the CNS that are typical of CNS inflammatory demyelinating disease, yet lacking symptomatic clinical features suggestive of MS. To more closely approximate real-world practice and facilitate early diagnosis, MRI anomalies will be required to meet dissemination in space criteria as defined by the 2017 McDonald diagnostic criteria for MS. Male and female patients aged 18–55 with a diagnosis of RIS in accordance with the McDonald 2017 criteria for DIS at screening will be eligible for this study.

As RIS is typically identified incidentally, first-degree family members of individuals with MS will be pre-screened for possible recruitment into this study. These relatives are at increased risk for RIS, with an estimated 3%–10% of clinically unaffected siblings having lesions highly suggestive of demyelination. After obtaining written consent, pre-

screening MRIs will be offered to such high-risk individuals and those who meet radiologic criteria will be eligible for the full study. Patients already diagnosed with RIS are also eligible for this study. Any known RIS patients whose MRIs have remained stable for 5 years or more will be excluded.

While younger age (<37) represents a significant predictor for the development of a first clinical event in RIS patients, RIS is often not diagnosed until later; indeed, in the recent ARISE clinical trial of RIS, the average age at diagnosis was around 44 years old (Okuda et al, 2022). Moreover, the ARISE trial found recruitment to be difficult and ultimately needed to end the study early for this reason. In order to effectively recruit for the CELLO trial, we will use the age range of 18-55, aligning with the phase 3 ocrelizumab trials in multiple sclerosis as well as the recent published study of RIS.

Pre-screened first degree family members who do not meet the McDonald 2017 criteria for DIS will be eligible to participate in a registry (Appendix 4). These individuals will have annual phone check-ins over the course of the total study duration to assess patient reported outcomes (Neuro-QoL; see Appendix 10) and healthcare utilization including neurologic or other autoimmune diagnoses, symptoms, medications (i.e., prescriptions, over-the-counter, supplements, etc.), number of emergency department visits, hospitalizations, office visits/physician encounters (i.e., specialists), etc.

Re-screening in general is not allowed, however patients enrolled in the registry may qualify for a re-screening opportunity at the discretion of the investigator. For more details on the registry of first-degree family members of patients with MS, see Appendix 4.

In the case of a clinical neurologic event consistent with CNS demyelination, the patient should have an unscheduled visit and a full assessment, as detailed in the SOA. Upon confirmation of a clinical relapse, the patient will be discontinued from the study and should start commercially available DMT, including ocrelizumab, at the discretion of the treating physician. In the event of radiologic progression, in which a new lesion suggestive of MS develops, the choice to continue or discontinue from the study in order to initiate treatment is at the discretion of the treating physician.

Treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the sponsor decides to close the trial, whichever occurs first.

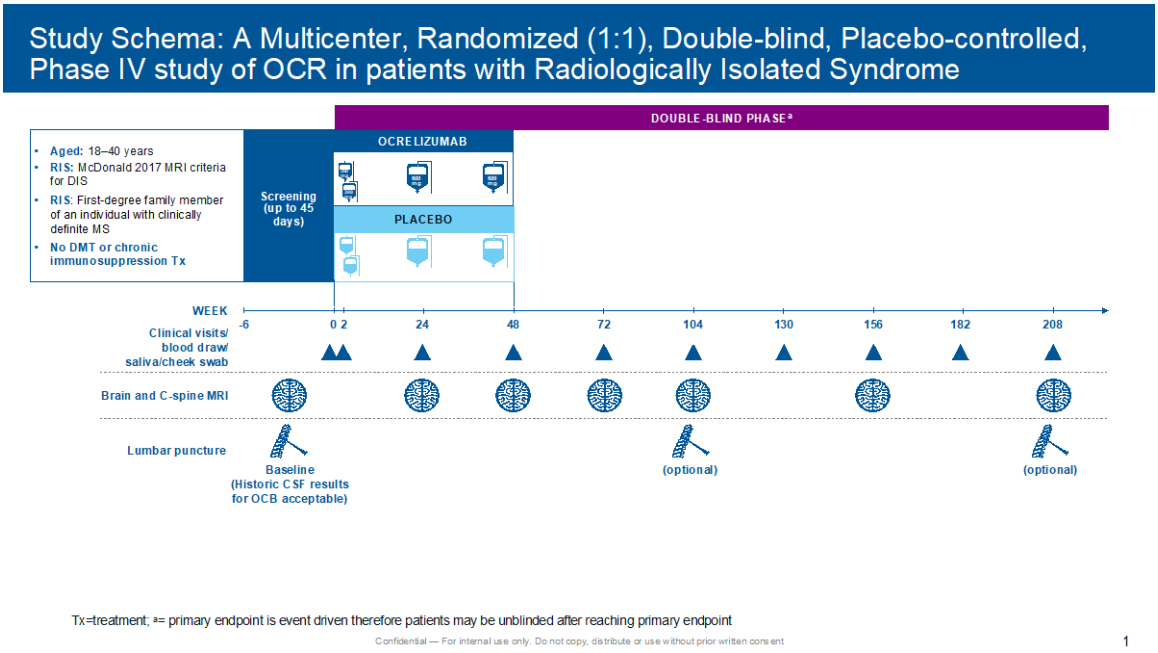
An external, independent DMC (iDMC) will periodically review safety data throughout the study until the primary analysis is performed. Following unblinding, iDMC involvement in safety monitoring is no longer needed. Analyses required for the iDMC data review will be performed as described in the iDMC Charter.

All patients enrolled into the main study will be evaluated for safety throughout the study. In the case of early termination, the patient will be asked to return for an early termination visit.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. The investigator will record reasons for screen failure in the screening log. Family members who undergo radiologic pre-screening and do not have lesions meeting DIS criteria are not considered screen failures and will be enrolled in the family registry.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 48 months/4 years after the last patient is enrolled.

In addition, the Sponsor and/or Collaborator (Genentech) may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 6–7 years.

RATIONALE FOR STUDY DESIGN

Rationale for Ocrelizumab Dose and Schedule

Consistent with the USPI, the ocrelizumab dose administered in this study is 600 mg every 24 weeks. Three-courses of ocrelizumab or placebo will be administered over the course of the study. The first dose of ocrelizumab will be administered as two 300 mg IV infusions on Week 0 (Day 1) and Week 2 (Day 15), with the subsequent second- and third-courses given as a single 600 mg infusion at Weeks 24 and 48. Study drug for patients randomized to the placebo group will be administered analogously to those receiving ocrelizumab. Patients will then be followed in the clinical trial for 3 years.

Administering three-courses of ocrelizumab permits the interrogation of the immunodynamics surrounding the emergence of CNS autoimmunity and the reconstitution of the immune system following anti-CD20 B cell depletion with ocrelizumab. Understanding the effect of B cell depletion in RIS using this treatment paradigm will provide invaluable insight into the onset of MS, as well as the mechanism of action of ocrelizumab, both of which remain poorly understood.

Rationale for Patient Population and Use of 2017 McDonald Criteria

When considering the pathophysiology of MS, and the increased emphasis placed on earlier identification of MS in order to initiate appropriate treatment early, it has been recommended that identical MRI criteria for DIS should be applied for the diagnosis of RIS and MS (De Stefano et al 2018; Flippi et al 2016). The original criteria for RIS required a fairly heavy lesion burden, whereas it has been suggested that RIS diagnostic criteria should instead reflect the 2017 McDonald criteria for DIS, which are routinely used for the clinical diagnosis of MS (Table 1). The McDonald criteria were revised in 2017 to increase sensitivity while promoting more rapid diagnosis of MS. In contrast to Okuda criteria, the McDonald criteria require fewer lesions and instead focus on lesion location rather than lesion count for the assessment of DIS, which facilitates interpretation and use in scenarios suggestive of MS. Therefore, the McDonald 2017 criteria for DIS represent the “real-world” criteria used routinely in everyday practice to establish MS diagnosis and share comparable sensitivity in detecting RIS, perhaps at even earlier stages of pathology. Patients meeting McDonald 2017 criteria for DIS can be confirmed to have MS at the time of their first clinical symptoms of disease. Early recognition of the disease provides the best window for treatment intervention. Thus, utilizing the 2017 McDonald criteria for DIS to establish RIS in this study may have clinical and research implications, not only in establishing an earlier window of opportunity to identify, diagnose and treat, but also in advancing the understanding of the onset and pathogenesis of disease.

Rationale for Control Group

To date, there are no expert guidelines on the management of RIS. The standard of care for RIS patients is active monitoring with periodical clinical and radiological follow-up every 6–12 months. This is in accordance with the MAGNIMS consensus recommendation published in 2018. Given that no standard of care therapy exists for the treatment of RIS, a placebo-control is considered to be appropriate for this trial.

Rationale for Biomarker Assessments

There is a paucity of evidence-based guidelines on the management of RIS and of factors that stratify risk for clinical MS in this population. Therefore, the discovery of biomarkers predictive of clinical conversion can guide clinical treatment decision-making, ultimately leading to risk-stratification for therapeutic interventions that maximize clinical benefit while minimizing patient harm. The identification of biomarkers reflecting MS disease biology in RIS not only represents a critical opportunity to better understand disease onset and progression, it also permits interrogation of the mechanism of action of ocrelizumab in this population.

Several studies have investigated biomarkers and risk factors associated with the development of a first clinical event in RIS patients. The presence of spinal cord lesions portends the greatest risk of conversion to clinical MS to date. Age (<40), sex (male) and the presence of infratentorial brain lesions have also been identified as putative risk factors to predict conversion to MS in RIS patients (Okuda et al. 2011, 2014; Etemadifar et al. 2014; Makhani et al 2019; Thouvenot et al. 2019). Abnormal CSF findings, including the presence of OCBs and/or elevated IgG index, have also been suggested as additional risk factors (Gastaldi 2017; Nakamura et al. 2014; Matute-Blanch et al. 2018; Makhani et al. 2019).

In the context of MS, biomarkers from the CSF are utilized as a surrogate for the CNS tissue (Comabella and Montalban 2014) and MRI of the brain and spinal cord is used as a non-invasive surrogate marker of disease activity (e.g., contrast-enhancing lesions; new and enlarging T2-weighted lesions). In particular, spinal cord MRI provides important additional information to brain MRI in understanding MS pathophysiology, allowing more accurate and earlier diagnosis of MS, and in identifying MS patients at higher risk of developing more severe disability. Advances in MRI techniques have enabled assessment of brain and spinal cord area and volumes. Changes in global and regional brain and spinal cord area (i.e., white and gray matter, thalamus) can be detected early in the disease course and are highly associated with disability progression and severity in MS as well as quality of life measures, including cognition and fatigue.

Studies have also focused on the evaluation of fluid biomarkers in RIS reflecting MS disease biology and suggest that these may also provide predictive value. In clinically definite MS, NfL has emerged as a leading candidate biomarker in blood and CSF. NFL correlates with disease activity, including Gd-enhancing MRI lesions and clinical relapses (Burman et al. 2014), as well as treatment response in RMS and PPMS (Gunnarsson et al. 2011; Axelsson et al. 2014). High levels of NfL in the CSF (Matute-Blanch et al 2018) and serum (Bjornevik et al 2019), have been identified in individuals with RIS and are associated with increased risk for the development of a first clinical neurologic event. Other key biomarkers of disease biology in MS that may be relevant to RIS include the presence of OCBs, or antibodies produced in the CSF (Link and Huang 2006), as well as the presence of intrathecal memory B cells, plasmablasts (Cepok et al. 2005), and the potent B cell chemoattractant CXCL13 (Piccio et al. 2010; Bankoti et al. 2014; Palanichamy et al. 2014; Stern et al. 2014). The presence of OCBs has been associated with a worse prognosis (Joseph et al. 2009; Winger and Zamvil 2016) and has been shown to have high predictive value for conversion from CIS to clinically definite MS (Tintore et al 2008; Dobson et al 2013), which may also be relevant to those with RIS (Matute-Blanch et al. 2018). Furthermore, it has been observed that the peripheral B cells of RIS patients are skewed toward a proinflammatory phenotype and are associated with worse prognosis. However, these biomarkers require further investigation in RIS as prior studies had relatively small sample size and short follow-up periods.

The research efforts in the present study are aimed toward the identification and verification of biomarkers, including neuroimaging, fluid/serologic, and immunologic, as well as clinical and paraclinical features that predict the evolution from RIS to a first neurologic attack and subsequent MS diagnosis. In addition, to better understand the mechanism of action of ocrelizumab in RIS, this study will assess the treatment effect of ocrelizumab on biomarkers of MS disease biology in the blood and CSF (i.e., OCBs, NfL, B cell subsets, MRI, etc.) Newly emerging biomarkers reflecting inflammation and neurodegeneration, such as cytokines, chemokines, antigen-specific B cells or T cells, and GFAP (glial fibrillary associated protein) will be evaluated and may provide insight into disease mechanisms and onset of clinical MS (Piccio et al. 2010; Barun and Bar-Or 2012; Alvermann et al. 2014; Hohmann et al. 2014). Elucidating these factors could significantly impact the management of patients with RIS, guide treatment decisions, and improve long-term outcomes while also advancing the science underlying MS pathogenesis and the emergence of CNS autoimmunity (Alshamrani 2017; Okuda 2017).

MATERIALS AND METHODS

PATIENTS

Approximately 100 patients will be enrolled in the main study.

Inclusion Criteria

Pre-Screening of First-Degree Family Members

Family members must meet the following inclusion criteria for pre-screening:

Signed informed consent form

First-degree family member of an individual with clinically definite MS

Age 18-55 years

No prior exposure to DMT or long-term immunomodulatory medications

Willingness to participate in full study protocol, if RIS is discovered

Screening

Patients must meet the following inclusion criteria for screening:

Signed informed consent form

One of the following:

- First degree family member of an individual with clinically definite MS who was identified to have CNS lesions meeting McDonald 2017 criteria for DIS during a pre-screening MRI.
- Established RIS diagnosis (i.e. CNS lesions consistent with MS, meeting McDonald 2017 criteria for DIS), either diagnosed within the last 5 years or known to have had accumulation of CNS lesions within the last 5 years.

Age 18-55 years

No prior exposure to DMT or long-term immunomodulatory medications

Willingness to participate in full study protocol

Randomization

Patients must meet the following criteria for study entry and randomization:

Signed Informed Consent Form

Aged 18–55 years at time of signing Informed Consent Form

Ability to provide written informed consent and be compliant with the study protocol

CNS lesions consistent with MS, meeting McDonald 2017 criteria for DIS

RIS diagnosis established within last 5 years OR with known accumulation of CNS lesions within last 5 years

No alternative diagnosis established during serologic workup for MS mimics

Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use one method of contraception with a failure rate of <1% per year or a barrier method supplemented with spermicide. Contraception must continue for the duration of study treatment and for at least 24 weeks after the last dose of study treatment.

- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause of other than menopause), and has not undergone surgical sterilization (removal of the ovaries and/or uterus)
- Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence and withdrawal are not acceptable methods of contraception.
- Examples of barrier methods supplemented with the use of spermicide include male or female condom, cap, diaphragm, or sponge.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from pre-screening, screening and randomization:

Intolerance to gadolinium-based contrast agent

Contraindications to MRI

≥5 years of radiologic stability since first known abnormal MRI, for patients previously diagnosed with RIS

History of remitting clinical symptoms consistent with MS lasting >24 hours prior to CNS imaging revealing anomalies suggestive of MS

CNS MRI anomalies are better accounted for by another disease process, for patients previously diagnosed with RIS

Infection Related

- Known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- History of recurrent aspiration pneumonia requiring antibiotic therapy

History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)

Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis or atypical mycobacterial disease, but excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit

Cancer Related

History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix or the uterus that have been excised and resolved with documented clean margins on pathology)

Pregnant or lactating, or intending to become pregnant during the treatment phase and 6 months after the last infusion of study drug

Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to initiation of study drug.

Other Medical Conditions

History of or currently active primary or secondary immunodeficiency

History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies

History of alcohol or other drug abuse within 24 weeks prior to enrollment

History or known presence of systemic autoimmune disorders associated with systemic symptoms (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren's syndrome, Behçet's disease)

Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study

Significant, uncontrolled disease, as defined by AMA guidelines or similar, such as cardiovascular (including congestive heart failure – NYHA grade 3 or 4, cardiac arrhythmia), uncontrolled hypertension, pulmonary (including chronic obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), gastrointestinal, or any other significant disease

Known presence or history of other neurologic disorders, including but not limited to, the following:

Progressive multifocal leukoencephalopathy, CNS or spinal cord tumor, potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)

History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS])

Neuromyelitis optica spectrum disorders (NMOSD)

Ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord

Severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Psychosis not yet controlled by a treatment

Drug Related

Systemic, high dose corticosteroid therapy within 4 weeks prior to screening

Contraindications for, or intolerance to, oral or IV corticosteroids, including IV methylprednisolone, according to the country label, including hypersensitivity to any of the treatment drug constituents

Prior exposure to immunomodulatory medications and/or DMT

Prior treatment with any disease modifying therapy for MS including but not limited to: interferon (IFN-β-1a (Avonex, Rebif), IFN-β-1b (Betaseron/Betaferon), glatiramer acetate, dimethyl fumarate (DMF; Tecfidera), diroximel fumarate (Vumerity®) fingolimod (Gilenya) or siponimod (Mayzent), ozanimod (Zeposia®) natalizumab (Tysabri), alemtuzimab (Lemtrada), cladribine (Mavenclad), rituximab (Rituxan), and other anti-CD20 agents

Previous treatment with cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation

Previous or concurrent treatment with any investigational agent or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)

Vaccinations: Receipt of a live or live-attenuated vaccine or an inactivated/non-live vaccine within 6 weeks prior to enrollment

Laboratory: Certain laboratory abnormalities or findings at screening, including the following:

Positive serum β-hCG

Positive for hepatitis B (hepatitis B surface antigen [HBsAg] positive or hepatitis B core antibody [total HBcAb] confirmed by positive viral DNA polymerase chain reaction [PCR])

AST or ALT $\geq$3.0 $\times$upper limit of normal

Total white blood cell count, including differential counts, below lower limit of normal

Absolute lymphocyte count below lower level of normal

Absolute neutrophil count below lower limit of normal

Platelet count below lower limit of normal

METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. IxRS will be used to assign study identification numbers at the time of signing an informed consent document; this includes close family members undergoing pre-screening as well as those with known RIS who are being screened for the randomized controlled trial. Eligible patients must be randomized through IxRS prior to receiving any study drug. Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study.

The randomization list will not be available to the study centers, monitors, or to the Sponsor project team. All individuals directly involved in the study will remain blinded to the treatment assignment.

The treatment code will be released to the study team to facilitate analysis of the biological samples collected during this study after the unblinding for the primary analysis has been completed.

Study site personnel and patients will be blinded to treatment assignment until after the primary analysis. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinded trial statisticians, clinical supply chain managers, sample handling staff, and IxRS service provider.

Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, an interactive voice or web-based response system (IxRS) will be used to assign a study identification number. After completion of screening procedures and assessments have been completed, and eligibility has been established for a patient, the IxRS system will be used to randomize the patient and receive treatment assignment.

Patients will be randomly assigned to one of two treatment arms: ocrelizumab or placebo. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- Presence of spinal cord lesions
- Presence of CSF oligoclonal bands

Results of a lumbar puncture/CSF oligoclonal banding analysis performed at baseline are required prior to randomization. A subset of study participants may have had lumbar puncture/CSF analysis performed previously. Such historic oligoclonal banding results may be used for the purpose of stratifying randomization with appropriate source documentation. For study participants who have previously had lumbar puncture/CSF analysis, all study lumbar punctures are optional.

For study participants who have never had a lumbar puncture/CSF analysis, this procedure is required prior to randomization. Additional lumbar punctures at weeks 104 and 208 are optional.

Blinding

This is an assessor blinded study. During the double-blind period, each site will have: a principal or Treating Investigator and an Examining Investigator or rater. Both the Treating and Examining Investigators will be blinded to treatment assignment.

The Treating Investigator is the physician responsible for the patient care and should be a neurologist experienced in the care of MS patients. The Treating Investigator will make treatment decisions based on the patient's clinical response and laboratory findings.

The Examining Investigator should be a neurologist or other health care practitioner and must be trained in administering the Neurostatus Functional System Scores (FSS) and Expanded Disability Status Scale (EDSS) examination prior to study start (Appendix 5).

The Examining Investigator will perform the neurological examination, document the FSS scores, and assess EDSS scores. The Examining Investigator or a qualified designee will also be responsible for performing and documenting results from the Symbol Digit Modalities Test. They will only have access to data from the assessments listed above. Every effort will be made to ensure that there is no change in the EDSS rater throughout the course of the study for any individual patient. Whenever possible, the same person should perform the examination for the full study duration.

All efforts should be made to keep the Examining Investigator blinded to the treatment assignment during the double-blind period. Patients will be instructed not to discuss any symptoms related to the study treatment with the Examining Investigator; the Examining Investigator should remind the patient at the start of the examination.

To prevent potential unblinding of the assigned arm in the double-blind treatment period as a result of adverse events or changes to laboratory results, the following, additional measures have been implemented:

Blinding of laboratory parameters: Laboratory parameters that may lead to unblinding to treatment assignment, such as fluorescence-activated cell sorting (FACS) cell counts including CD19+ cells, lymphocyte count, IgM and IgG levels, will be blinded in all

patients. In order to ensure patients' safety in the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and Medical Monitors with reflex messages triggered by critical blinded laboratory results. Investigators notified of their patient's critical laboratory test results will be instructed to suspend further treatment with study drug until the patient becomes eligible for re-treatment. The reflex messages from a central laboratory, together with non-blinded laboratory results, should be carefully reviewed at every visit before continuing with study treatment. The reflex messages will occur during the double-blind, period. During the treatment period, patients will be assessed at clinical visits as per Schedule of Assessments.

Prior to the next infusion of study drug, patients will be evaluated for pre-specified conditions and laboratory abnormalities to allow for re-treatment.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.5) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

STUDY TREATMENT

The investigational medicinal product (IMP) for this study is ocrelizumab.

Study Treatment Formulation, Packaging, and Handling

Ocrelizumab and Placebo

Ocrelizumab will be supplied by Genentech in 15 cc Type I glass vials as a sterile, single-use solution for IV infusion and contains no preservatives. Each vial contains 300 mg of ocrelizumab, at a nominal fill volume of 10 mL. The drug product is formulated as 30 mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic,

low-protein-binding filter (pore size of 0.2 micrometer or less). For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure, local prescribing information, and Drug Preparation Guidelines.

Placebo for this trial will be supplied by Genentech. It is a preservative-free, sterile, colorless to pale yellow solution supplied in 15-cc single-dose glass vials with 20 mm stoppers. Vials are filled to enable delivery of 10.0 mL of Ocrelizumab Placebo. Ocrelizumab Placebo is composed of the same formulation as the study drug, but does not contain the study drug. Density of Ocrelizumab Placebo is 1.01 g/mL.

Non-Investigational Medicinal Products

In this study, non-investigational medicinal products will include premedication to the study drug infusion. The following premedication will be used:

Mandatory methylprednisolone (or an equivalent)

Mandatory antihistaminic drug (e.g., diphenhydramine)

Recommended oral analgesic/antipyretic (e.g., acetaminophen)

Refer to Section 0 for further details on premedication administration.

Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF).

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.3.2.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

Ocrelizumab and Placebo

The ocrelizumab dose administered will be 600 mg every 24 weeks. The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart (Weeks 0 and 2). For the subsequent doses, ocrelizumab will be administered as a

single 600-mg IV infusion every 24 weeks (Weeks 24 and 48). A minimum interval of 22 weeks must be maintained between each dose of ocrelizumab.

Each ocrelizumab dose should be administered according to the guidance provided in the most current USPI (https://www.gene.com/download/pdf/ocrevus_prescribing.pdf).

Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs.

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

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

Premedications

Methylprednisolone has been shown to decrease the incidence and the severity of infusion reactions. An integrated analysis of patients with MS treated with ocrelizumab revealed that the addition of antihistamines pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold. All study patients will receive premedications according to the guidelines outlined in the USPI (https://www.gene.com/download/pdf/ocrevus_prescribing.pdf).

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

Re-Treatment Criteria for Ocrelizumab

Prior to re-treatment with study drug, patients will be evaluated for the following conditions and laboratory abnormalities. If any of these are present prior to re-dosing,

further administration of study drug should be suspended until these are resolved or held indefinitely:

Life-threatening (Grade 4) infusion-related event that occurred during a previous study drug infusion

Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality

Active infection

Ongoing pregnancy

Investigational Medicinal Product Accountability

All IMPs required for completion of this study (ocrelizumab/placebo) will be provided by Genentech where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by Genentech, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the drug depot with the appropriate documentation. The site's method of destroying Genentech-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

Continued Access to Ocrelizumab

Currently, Genentech, a member of the Roche Group, does not have any plans to provide Genentech IMP (ocrelizumab) or any other study treatments to patients beyond the second-year extension of the study or the 2 year sub-study. Genentech may evaluate whether to continue providing ocrelizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days

prior to initiation of study drug or ongoing therapy (e.g., physiotherapy) to the study completion/discontinuation visit. All such medications and therapies (including their indication) should be reported to the investigator and recorded on the appropriate eCRF.

Treatment of First Clinical Neurologic Event

In the case of the development of an acute or progressive clinical neurologic event consistent with CNS demyelination during study, the patients should have an unscheduled visit and a full assessment, as detailed in the SOA. As described in Section 4.5.12 a neurologic event consistent with CNS demyelination for this study is defined as the occurrence of new and/or worsening neurological symptoms suggestive of MS that persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications). In the case of an acute syndrome, it should be immediately preceded by a stable or improving neurological state for least 30 days. In some rare cases a progressive clinical syndrome (e.g., leg weakness, cognitive impairment, EDSS worsening) may develop with a temporal profile revealing at least 12-months of neurologic deficit as per the treating physician's judgement. The new or worsening neurological symptoms must be adjudicated by a Sponsor-appointed adjudication committee, comprised of three expert neuroimmunology clinicians, who will review documentation associated with the event and confirm whether a relapse has occurred. Confirmed relapses will contribute to the primary endpoint.

The patient may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 1 g/day IV methylprednisolone for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. After a confirmed clinical relapse, patients will be discontinued from the study and start commercially available DMT approved for MS, including ocrelizumab, at the discretion of the treating physician. Whether patients continue or discontinue the treatment based on the occurrence of a neurologic event consistent with MS is at the discretion of the treating physician and the patient, and whether the patient or investigator feels he or she has met the criteria for withdrawal.

Treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the sponsor decides to close the trial, whichever occurs first.

Treatment of Radiologic Event

In the event of radiologic progression, in which a new contrast-enhancing or T2-weighted lesion suggestive of MS develops, the choice to continue or discontinue from the study

in order to initiate treatment with a DMT, including commercial OCREVUS®, is at the discretion of the treating physician. If a commercial disease modifying therapy is initiated, the participant will be discontinued from all study-related treatments. Regardless of whether the participant is started on commercial disease modifying therapy, individuals with a radiologic event should complete study assessments until they have completed week 208 or until they have had a confirmed clinical relapse, whichever occurs first.

As described above in Section 4.4.1 treatment may be stopped at any time due to lack of clinical benefit, unacceptable toxicity, withdrawal of consent, patient or physician decision to discontinue treatment, death, or if the sponsor decides to close the trial, whichever occurs first.

Prohibited Therapy

The following therapies for MS are not permitted during the treatment portion of the study (through week 72): Other B-cell targeted therapies (e.g., rituximab, atacicept, belimumab, or ofatumumab, etc.), natalizumab, fingolimod, siponimod, alemtuzumab, daclizumab, cladribine, teriflunomide, dimethyl fumarate ,diroximel fumarate ozanimod, interferons, glatiramer acetate, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation, IV Ig, plasmapheresis, other approved or investigational therapies for MS.

After patients have completed (or discontinued) treatment with study drug, they may receive alternative treatment for MS as judged clinically appropriate by the investigator. However, as sufficient data are not available regarding risks associated with switching to other products, the following recommendations are given:

Caution is advised if patients remain B-cell depleted.

Because of the unknown safety risk of administering disease-modifying treatments for MS after discontinuation of ocrelizumab, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine, cladribine, daclizumab, etc.) are strongly discouraged for as long as the patient remains B cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection).

Immunizations

Physicians are advised to review the immunization status of patients who are considered for treatment with ocrelizumab and follow local/national guidance for adult vaccination against infectious disease. Immunizations should be completed at least 6 weeks prior to first administration of ocrelizumab.

Non-live vaccines may be administered while on ocrelizumab if deemed clinically necessary. Vaccination study results (VELOCE) show that patients treated with ocrelizumab were able to mount an attenuated immune response to non-live vaccines and new antigens at week 12 after ocrelizumab infusion compared to placebo. However, no data are currently available to show if the same applies also to the SARS-CoV-2 vaccines. Treatment decisions should be made between a patient and their treating neurologist or other medical professional based on a benefit/risk assessment specific to the individual patient, and vaccines must be given in accordance with the approved label for the vaccine. The best time point for a vaccination in the interval between two ocrelizumab dosings is not known and might also be dependent on the individual risk of SARS-CoV-2 infection of the patient. In VELOCE, vaccinations started at least 12 weeks after the last infusion of ocrelizumab. Like for patients starting on ocrelizumab in a clinical study, a time window of at least 6 weeks before the next ocrelizumab infusion seems appropriate to allow the B cells generated to the vaccine to get established and develop into antibody producing plasmablasts or plasma cells that do not express CD20 and are therefore preserved once the next dose is given.

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette-Guerin, typhoid, yellow fever, vaccinia, cold-adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended during ocrelizumab treatment period and for as long as the patient is B cell depleted.

Data from the ocrelizumab Phase II and III program currently show that over 2 years after treatment with ocrelizumab, the proportions of patients with positive antibody titers against Streptococcus pneumoniae, influenza, mumps, rubella, varicella, and tetanus toxoid were generally similar to the proportions at baseline.

Of note: for seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Please refer to the current version of the Ocrelizumab Investigator's Brochure for further guidance and updates on immunization.

STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Overview of Clinical Visits

After the screening, patients who fulfill the entry criteria will be scheduled for baseline assessments. Visits will take place as described in Appendix 1.

Visits should be scheduled with reference to the date of the baseline visit (Day 1). A minimum interval of 22 weeks should be maintained between each infusion.

At infusion visits, it is anticipated that the patients will have to stay at the hospital or clinic for a full day. Patients treated with ocrelizumab should remain under observation for at least 1 hour after the completion of the infusion. If for logistical reasons the infusion cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the patient still meets re-treatment criteria.

Patients who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 4.5.3). Additional unscheduled visits for the assessment of disease worsening, new neurological symptoms, or safety events may occur at any time.

Patients who are pregnant or breastfeeding should continue to follow the schedule of activities; however, no infusions will occur. If there is a concern regarding the ability of a pregnant or breastfeeding patient to complete all scheduled assessments, or if assessments are contraindicated with pregnancy, the investigator must contact the Medical Monitor for further discussion.

Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in the schedules of activities (see Appendix 1). Thus, a patient who had all assessments of a dosing visit performed, but could not receive the infusion, should be rescheduled for the infusion on another day. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated.

Unscheduled Visits

Patients who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their pre-planned, scheduled study visits and regardless of the study period. The EDSS assessment

should be performed for any suspected neurological worsening. If an MS relapse is diagnosed or suspected, EDSS assessment should be performed within 7 days, in addition to completing the appropriate eCRF.

Other assessments (e.g. MRI) performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient, and would be covered clinically, rather than by the research study. The primary reason for performing an unscheduled visit will be reported in the eCRF.

Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), general cancer risk factors, breast cancer-specific risk factors, reproductive status, smoking history, lumbar puncture history, sleep status and smoking status, will be recorded at baseline.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment and ongoing therapies (e.g., physiotherapy including its indication) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained, and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

Physical Examinations

A complete physical examination performed at screening should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height and weight will be measured per the appropriate schedule of activities.

Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a seated position, pulse rate, and temperature.

On the infusion days, blood pressure, pulse rate, and temperature should be taken within 45 minutes prior to the premedication (methylprednisolone) infusion and recorded on the appropriate eCRF. Temperature should be measured and recorded in patient's notes only.. Vitals will be monitored during infusions of study drug according to the prescribing information. Clinically significant abnormalities should be recorded on the Adverse Event or Infusion-Related Reaction. In the event of an IRR or if clinically indicated, additional vital signs readings (e.g., blood pressure and pulse rate) should be taken during and post-infusion at the discretion of the investigator and should be recorded on a dedicated Vital Sign eCRF.

Neurological Examination

A neurological examination will be performed at every planned visit. During an unscheduled visit, the neurological examination will be performed only if deemed necessary.

In the presence of newly identified or worsening neurological symptoms at any given time in the study, a neurological evaluation should be scheduled promptly and performed within 7 days of onset of the new or worsening neurological symptom(s).

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). A brain MRI scan and CSF analysis may be warranted to assist in the diagnosis of PML. Refer to Appendix 7 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurological symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Appendix 7). The Medical Monitor should be immediately contacted by telephone and email.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.1.2).

Brain and Cervical Spine Magnetic Resonance Imaging

Pre-screening of family members:

Pre-screening brain MRIs without contrast will be performed for asymptomatic close family members who otherwise qualify for the study and would like to participate. The study investigator, or designee, will interpret pre-screening MRI brains to make a

determination about whether they meet McDonald 2017 criteria for dissemination in space. Pre-screening MRIs have limited sequences, and as such, are not intended to identify non-MS pathologies. Participants will be informed if they meet criteria for RIS. Otherwise, any incidental findings would be handled at the discretion of the study investigator

Randomized clinical trial:

MRI will be used to monitor CNS lesions related to MS pathology and potentially other pathology findings. Brain and cervical spine (C-spine) MRI scans ± Gd will be obtained at study visits as shown in the schedule of activities (see Appendix 1). The evaluation of scans for incidental pathology not related to MS, such as migraine, PML, etc., is a local responsibility that should be handled according to the local practice. Any clinically significant findings should be reported on the Adverse Event eCRF.

MRI scans will be read by a centralized reading center for efficacy endpoints. Prior to initiation of treatment on Day 1/Baseline, a quality control (QC) report for the patient's Screening MRI scan must have been received from the centralized reading center confirming scan passed QC as well as an MRI Eligibility Report to confirm eligibility for the study. The brain MRI requires approximately 2 business days from scan receipt to be quality checked before dosing of ocrelizumab. Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI scanner are described in a separate MRI technical manual.

In general, focal white matter lesions of vascular origin can be more prevalent in young adults and migraineurs compared to demyelinating lesions. These lesions display different morphological and topographic characteristics compared to typical demyelinating lesions observed in MS.

Assessment of Disability: Expanded Disability Status Scale

Disability in MS is commonly measured by the EDSS (Appendix 5). EDSS will be administered by the Investigator or a qualified designee under the supervision of the investigator at the timepoints indicated in the schedule of activities (see Appendix 1). Additional EDSS assessments for individual patients may be requested between visits, (e.g., at the time of development of new radiologic evidence of MS, clinical neurologic event, etc.).

The EDSS is based on a standard neurological examination, incorporating functional systems (pyramidal, cerebellar, brainstem, sensory, bowel, and bladder, visual, and cerebral [or mental]) and ambulation rated and scored as FSS. Note that the following item need not be scored: sexual dysfunction. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations

and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011).

Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) has demonstrated sensitivity in detecting not only the presence of cognitive impairment but also changes in cognitive functioning over time (i.e., information processing speed) and in response to treatment. Several studies have demonstrated that RIS is associated with cognitive impairment and dysfunction similar to that of patients with clinical MS. Further, substantial evidence suggests that cognitive problems present in early in MS before any apparent symptoms cross the clinical threshold.

For consistency, it is recommended at each visit the same examiner administer the SDMT with the same patient. A four-point decrease in SDMT score is considered clinically relevant/meaningful change.

The oral version of the SDMT should be used for all CELLO-related visits.

Assessment of Neurologic Event

Patients will be evaluated for development of a clinical neurologic event consistent with CNS demyelination by the Treating Investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm the same occurring between the visits.

All new or worsening neurological events consistent with MS are to be reported in the appropriate eCRF. EDSS should be performed within 7 days from the onset of the clinical neurologic event.

For this study, a neurologic event consistent with CNS demyelination is defined as the occurrence of new and/or worsening neurological symptoms suggestive of MS. Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications) and be immediately preceded by a stable or improving neurological state for least 30 days. The new or worsening neurological symptoms must be adjudicated by a Sponsor-appointed adjudication committee, comprised of three expert neuroimmunology clinicians, who will review documentation associated with the event and confirm whether a relapse has occurred. Confirmed relapses will contribute to the primary endpoint.

Investigators will also screen patients for signs and symptoms of worsening neurological function localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with

suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing (see Appendix 7). A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.

If an investigator determines that further testing (e.g. MRI) is necessary to evaluate a neurologic event, this would be performed according to standard of medical care. Results from any clinically warranted MRIs will be recorded in the eCRF.

Clinical neurologic events (i.e., regardless of whether they meet criteria for a protocol-defined neurologic event) will be recorded in the eCRF.

Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests will collected on the days indicated in the schedule of activities (see Appendix 1).

Pre-infusion laboratory test results need to be available for review before each infusion, unless otherwise specified.

Samples for the following laboratory tests will be sent to the sites' local laboratory for analysis according to the appropriate SOA unless otherwise indicated (further details will be provided in the laboratory manual).

Hematology: hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count

Quantitative Immunoglobulin (local lab evaluation at screening visit only): Ig levels (including Total Ig, IgG, IgM, and IgA isotypes).

Blood chemistry: AST, ALT, total bilirubin, urea or BUN, creatinine, potassium, sodium, calcium

Urinalysis**:** A urine dipstick will be performed at the site (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and applicable will be performed at the site

Pregnancy test: All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

All women of childbearing potential must have regular pregnancy tests. A urine pregnancy test (sensitivity of at least 25 mU/mL β-hCG) will be performed locally at the timepoints shown in Appendix 1. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone infusion. A positive urine pregnancy test

should be confirmed with a serum test through the central laboratory prior to any further dosing with study drug. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed by the central laboratory.

Viral serology and detection: All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by PCR must be negative to be eligible.

Liver function (i.e., ALT/SGPT, AST/SGOT, total bilirubin) should be reviewed throughout the study. Patients who develop evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded. Patients who develop hepatitis B should be withdrawn from the study treatment. Should treatment for hepatitis be prescribed, this will be recorded in the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume study treatment after recovery.

Samples for the following laboratory tests and biomarkers will be sent to the central laboratory and/or to the Sponsor or designated processing site, and may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (CRO and/or academic research laboratories affiliated with the study):

Quantitative immunoglobulin: Ig levels (including total Ig, IgG, IgM, and IgA isotypes)

Blood TBNK/B-cell subset panel sample for CD19 and other circulating B-cell subsets, T cell subsets, and other innate immune cells, including NK cells, neutrophils, monocytes, etc.

Serum: analysis may include but will not be limited to levels of soluble markers of acute injury, disease activity and neurodegeneration (i.e., NfL, GFAP) and/or inflammatory markers (i.e., CXCL13, BAFF (B cell activating factor), etc.); other disease associated markers (i.e., serum Vit 25 [OH] D); and the relationship between ocrelizumab exposure and selected pharmacodynamics

Blood samples for RNA extraction for exploratory research on non-inherited biomarkers, which may include but not be limited to immune gene expression markers

Peripheral blood mononuclear cells (PBMCs): analysis may include but will not be limited to B- and T-cell numbers, other cell types, activation markers, functional attributes, activity, and/or molecular status of cells; and levels of soluble inflammatory markers, such as TNF, IL-6, IL-10, IL-17, interferon-gamma, soluble CD27 (sCD27), and other cytokines and chemokines, etc.

Exploratory biomarker research may include, but will not be limited to, the assessments listed above. Oral samples (gingival swabs) will be stored for future analysis, including evaluations of the microbiome in early MS. Given the complexity and exploratory nature

of biomarker analyses, results from the analyses will not be shared with investigators or study participants, unless required by law.

In the case of suspected PML, stored serum or plasma biomarker may be used to assess status of JC virus (JCV) antibodies.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

CSF: A CSF specimen will be collected at baseline for all participants who have not previously undergone this testing. CSF will be tested for cell count, protein, elevated IgG index and one or more IgG oligoclonal bands using the local lab. The remainder of this CSF sample will be retained as a biomarker sample, and analysis may include, but will not be limited to NfL and adaptive and innate immune cell subsets. Levels of soluble neurodegeneration markers, and/or inflammatory markers; and the relationship between ocrelizumab exposure and selected pharmacodynamics. Fluoroscopy can be used, if required, for the LP to draw the CSF.

Certain analyses may be conducted at study sites as directed by the Sponsor, or the sample may be shipped to the central laboratory and/or to the Sponsor or designated processing site, and may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (CRO and/or academic research laboratories affiliated with the study).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

Plasma and/or serum and/or whole blood samples or their derivatives (e.g. peripheral blood mononuclear cells, PBMC) collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed unless the patient has consented for their transfer to the Research Biosample Repository (RBR, described in Section 4.5.19 below).

Any leftover CSF samples that were collected for IgG index/OCB analysis to determine eligibility for patients who did not have historical data and the Week 48 CSF sample will be destroyed no later than 5 years after the final Clinical Study Report has been completed or until exhausted, or earlier depending on local regulations unless the patient has consented for their transfer to the RBR.

Oral samples (gingival swabs) will be destroyed no later than 5 years after the final Clinical Study Report has been completed or until exhausted, or earlier depending on local regulations unless the patient has consented for their transfer to the RBR.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 4.5.19.2 and Section 8.4.

Hepatitis Screening and Liver Function Monitoring

Patients with recurrent or chronic hepatitis B or history/presence of hepatitis C infection must be excluded from enrollment into the study. Hepatitis B and C serology will be performed at screening.

A positive result to either HBsAg, total HBcAb associated with positive viral DNA titers as measured by PCR, or a positive result for HepCAb should result in the patient's exclusion.

Patients with evidence of past resolved hepatitis B infection (i.e., positive total HBcAb associated with a negative viral DNA) can be enrolled and will have the hepatitis B viral DNA checked regularly as per the schedule of activities (see Appendix 1).

Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further ocrelizumab infusions.

Liver function (i.e., ALT, AST, alkaline phosphatase, and total bilirubin) should be reviewed throughout the study. Patients developing evidence of liver dysfunction should be assessed and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded.

Patients developing hepatitis B or C should be withdrawn from the study. Should treatment be prescribed, this will be recorded on the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after the patient's recovery.

Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be elicited from patients in this study to better characterize patient quality of life while on ocrelizumab compared to placebo for patients with RIS. The Neuro-QoL, (Quality of Life in Neurological Disorders) will also be used in this study to examine patient-reported measures of physical function, emotional and cognitive health as well as social abilities. The National Institute of Health's Neuro-QoL™ represents a comprehensive system of PRO measures that target neurologic disorders, including MS, and encompasses a series of short forms that measure physical, social, and mental domains of health-related quality of life.

The Neuro-QoL™ is required to be administered prior to administration of study drug and prior to any other study assessment(s) to ensure the validity of the instruments is not compromised. Also note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Due to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events.

PRO instruments will be completed to assess the treatment benefit and more fully characterize the safety profile ocrelizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with ocrelizumab. For further information, see Appendix 10 for the Neuro-QOL.

Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets or digitally to enable the instrument to be administered at each specified timepoint. Any hardcopy booklets will be labeled with the timepoint of administration.

During clinic visits PRO instruments should be administered as outlined below:

Patients' health status should not be discussed prior to administration of the instruments.

Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

Sites should allow sufficient time for patients to complete the instruments, estimated to be 5–10 minutes

Sites should administer the instruments in a quiet area with minimal distractions and disruptions.

Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

Site staff should not interpret or explain questions, but may read questions verbatim upon request.

Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS to identify variants that are predictive of response to study drug, are associated with progression RIS to clinical MS, progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this section of the protocol will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 0 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

Optional Lumbar Punctures

Consenting patients will undergo optional lumbar punctures at baseline, week 104, 208, and any unscheduled visits. CSF will be processed and stored, or used for 10X single cell sequencing and other advanced immunologic analyses (if patient/site is participating in the Immune Cell Network Sub-study). Blood will always be processed (for peripheral blood mononuclear cells) and either tested (e.g. with 10X single cell sequencing) or stored in parallel to any CSF collections.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional lumbar punctures. A separate, specific signature will be required to document a patient's agreement to undergo optional lumbar punctures. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent in the appropriate eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.19. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 0 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

Optional Samples for Immune Cell Network Sub-study

Consenting patients will undergo blood draws in parallel with CSF at baseline. Longitudinal samples will be obtained from sub-study participants who consent to one or more additional lumbar punctures. For these participants, paired blood and CSF will also be collected at week 104 and/or 208 (participants may consent to one or both optional

LPs). Blood will always be processed (for peripheral blood mononuclear cells) and either tested (e.g. with 10X single cell sequencing) or stored in parallel to any CSF collections.

The Informed Consent Form will contain a separate section that addresses optional blood for the Immune Cell Network Sub-study. A separate, specific signature will be required to document a patient's agreement to undergo optional lumbar punctures. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, in the appropriate eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.19. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.19 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

See

Appendix 2 for additional information.

Optional Samples for Research Biosample Repository

Use and storage of RBR samples (which may include leftover samples and/or samples collected specifically for the RBR) is summarized below:

Who can use the samples?	The study team/program has use of the samples and can decide if and when other researchers can use the samples.
When are the samples available for analysis?	Samples can be analyzed any time during or after the study, until the samples are used up or no longer needed (or as outlined in the locally approved version of the RBR ICF).
What type of research is allowed?	The samples can be used for study-specific research or for extended research as outlined in the RBR section of the ICF.
Who manages the samples?	Samples are managed by Yale University in collaboration with Genentech.
Where are the samples stored?	During the study, samples are usually managed by a central laboratory. No later than the time of study closure, samples are transferred to Yale University and/or Genentech for ongoing management.

Sample Collection

For all patients consenting to participate in the RBR, any biospecimens not directly utilized during this study will be transferred to the RBR no later than at the end of the study.

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ocrelizumab, neurologic or immune/inflammatory diseases, or drug safety:

Blood samples collected at Baseline, Week 24, Week 48, Week 72, Week 104, Week 130, Week 156, Week 182, Week 208, Unscheduled, and Discontinuation visits.

Leftover blood, serum, PBMC samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

Gingival swab samples

Any remaining CSF specimens

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing

researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

Consent to Participate in the Research Biosample Repository

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples remaining unused at the conclusion of the study will be stored in the Yale Data Registry & Research Biorepository. These samples could be used to research other

neurologic, inflammatory or immune conditions in the future. Samples in the Data Registry & Biorepository will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

When the study is completed, further access to biologic samples will be provided through the Yale Data Registry & Biorespository.

Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

MSResearch@yale.edu

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

TREATMENT, PATIENT, AND STUDY DISCONTINUATION

Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

Additionally, patients must be withdrawn from treatment under the following circumstances:

- Life-threatening (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Demonstrate active hepatitis B infection, either new onset or reactivation
- PML
- Newly diagnosed malignancy
- Patients who become pregnant /or lactating
- Patients who decide to discontinue treatment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

If a patient meets any of the treatment withdrawal criteria (see above), the patient must be withdrawn from treatment. Patients who prematurely withdraw from study drug treatment will need to return to the clinic for an unscheduled treatment discontinuation visit (see Appendix 1 for additional details). After treatment discontinuation, every effort should be made to have the patient enter the follow-up phase of the study.

For patients who have withdrawn from study drug treatment, the investigator should decide as to further treatment of the underlying disease (see Section 4.4 for recommendations on alternative treatments for MS post-ocrelizumab).

Patient Discontinuation from the Study

Patients will return to the clinic for an end of observation or withdrawal from follow-up visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If patient is lost to follow-up, the investigator should make every effort to contact the patient by telephone to establish as completely as possible the reason for the withdrawal.

Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

ASSESSMENT OF SAFETY

SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ocrelizumab in completed and ongoing studies. The anticipated important safety risks for ocrelizumab are outlined below. Please refer to Ocrelizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Risks Associated with Ocrelizumab

Important, identified, and potential risks associated with ocrelizumab are described in the approved risk management plan, and provided below. Please refer to the most recent version of the Ocrelizumab Investigator's Brochure for updates on risks associated with ocrelizumab treatment.

Identified Risks and Adverse Drug Reactions
Infusion-Related Reactions

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to the following: pruritus, rash, urticaria, erythema, bronchospasms, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis.

Patients should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR. Patients will be informed about delayed post-infusion symptoms and instructed to contact the study physician if he or she develops such symptoms.

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

For further guidance on how to manage IRRs please refer to the current Ocrelizumab Investigator's Brochure.

Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections. Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5%–6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of patients with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the interferon β-1a group (2.9%); in PPMS, the proportion of patients with serious infections was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group.

Serious, opportunistic and fatal infections have occurred in patients with lupus and rheumatoid arthritis treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab Investigator's Brochure.

No opportunistic infections were reported by any patient with MS treated with ocrelizumab during the controlled period of the pivotal trials.

In interventional clinical studies, there were no reports of hepatitis B reactivation in patients with MS treated with ocrelizumab, but it had been reported in 1 patient with rheumatoid arthritis treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active HBV should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

For PML see Potential Risks Section 5.1.1.2 below.

Impaired Response to Vaccination

After treatment with ocrelizumab for over 2 years in pivotal clinical trials, the proportion of patients with positive antibody titers against *Streptococcus pneumoniae*, mumps, rubella, and varicella were generally similar to the proportions at baseline.

The results of the randomized, open-label Phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raised adequate humoral responses to selected

vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit blunted, to tetanus toxoid; 23-valent pneumococcal polysaccharide; keyhole limpet hemocyanin neoantigen; and seasonal influenza vaccines. The results are summarized in the current version of the Ocrelizumab Investigator's Brochure.

Investigators should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients who are on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

Due to the potential depletion of B cells in neonates and infants of mothers who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B cells have recovered; therefore, measuring CD19-positive B-cell level in neonates and infants prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule, and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased.

Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total Ig over the controlled period of the studies, mainly driven by reduction in IgM. The proportion of patients with decrease in Igs below LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out.

Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)

Based on additional patient exposure an association between decrease in immunoglobulins and serious infections with ocrelizumab treatment was observed and was most apparent for IgG. There was no difference in the pattern (type, latency, duration, outcome) of the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.

Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days posttreatment (first timepoint of assessment) as an expected pharmacologic

effect. This was sustained throughout the treatment period. The longest follow-up duration after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B cells was 72 weeks (range 27–175 weeks). Patients with prolonged B-cell depletion should be monitored until his or her B cells have repleted.

Potential Risks

Progressive Multifocal Leukoencephalopathy

It has been reported in patients receiving ocrelizumab but only in patients where other contributory factors were present, such as prior immunosuppressive treatment (for example natalizumab or fingolimod). Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently.

Refer to Appendix 7 for guidance for diagnosis of PML. Please see the Ocrelizumab Investigator's Brochure for more details.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms.
A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Malignancies (including Breast Cancer)

An increased risk of malignancy with OCREVUS may exist. In controlled trials in MS, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

Refer to the current Ocrelizumab Investigator's Brochure for more details.

Neutropenia

In the controlled treatment period, decreased neutrophils were observed in 12% and 15% of MS patients treated with ocrelizumab in PPMS and RMS, respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. Based on

additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.

Additional information can be found in the current Ocrelizumab Investigator's Brochure.

Risks Associated with Corticosteroids

The adverse reactions of corticosteroids may result from unwanted glucocorticoid actions or from inhibition of the hypothalamic-pituitary-adrenal axis. Please refer to local prescribing information.

Risks Associated with Antihistamines

The adverse reactions depend on the sedating properties of the antihistamine and include, but are not limited to, nausea, drowsiness, headaches, dry mouth, and allergic reactions such as rash. Please refer to local prescribing information.

Management of Patients Who Experience Adverse Events

Dose Modifications

Study drug dose modifications are not foreseen.

Treatment Interruption

Study drug treatment may be temporarily suspended in patients who experience relevant adverse events considered to be related to study drug and prevent the patient from re-treatment with the study drug (see Section 4.3.2.3 for details on re-treatment criteria).

For female patients who become pregnant during the study, study drug treatment will be discontinued upon confirmation of pregnancy. Study drug will not be re-started, but the patient should continue with other study-related visits and assessments, unless they are contraindicated due to pregnancy.

Management Guidelines Infusion-Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare cases, ocrelizumab treatment may need to be discontinued. Please also follow ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms (see also Table 2 for grading of intensity of IRRs).

For a **mild to moderate (Grade 1 or 2)** non-allergic, infusion-related event, the infusion rate should be reduced to half the rate being given at the time of onset of the event (e.g., from 50 mL/hr to 25 mL/hr or from 100 mL/hr to 50 mL/hr). Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the next closest rate on the patient's infusion schedule and the rate increments resumed.

For a **severe infusion-related event (Grade 3)** or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after all the symptoms have disappeared. The initial infusion rate at restart should be half of the infusion rate that was in progress at the time of onset of the reaction.

For a **life-threatening infusion-related event (Grade 4**) during an infusion, the infusion should be immediately stopped, and the patient should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). The patient will be withdrawn from treatment and should enter the follow-up phase.

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion but not the total dose.

SAFETY PARAMETERS AND DEFINITIONS

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).

Adverse Events of Special Interest

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 $\times$ ULN in combination with total bilirubin $>$ 2 $\times$ ULN

Treatment-emergent ALT or AST $>$ 3 $\times$ ULN in combination with clinical jaundice

Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

There are no Ocrelizumab Events of Special Interest.

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 AEs and SAEs as described in Section 5.2 where the patient has been exposed to Genentech product must be reported. Reporting period begins after informed consent is obtained and initiation of study treatment and ends 24 weeks 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., cancer diagnosed 2 days after first dose of OCRELIZUMAB).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I. or current 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.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted. Examples of non-directive questions include the following:

"How have you felt since your last clinic 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.

Diagnosis versus 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.

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), 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”.

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”).

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

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. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 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 (see Section Procedures for Eliciting, Recording, and Reporting Adverse Events5.4 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

Assessment of Causality of Adverse Events

Pregnancies

If a female subject becomes pregnant while receiving the study drug or within *24 weeks* 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 *24 weeks* a report

should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur, and on a voluntary basis we will follow the health of children through 1 year (Appendix 9). 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.

Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- 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

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.

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior 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 patient who participated in the study, this should be reported as an SAE adequately to Genentech Drug Safety during the follow-up period..

ADVERSE EVENT REPORTING

The investigational site is responsible for forwarding 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) to the sponsor within 24 hours of awareness.

It is understood and agreed that the Sponsor will be responsible for the collection and evaluation of AEs, SAEs, AESIs, Special Situation reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

Serious Adverse Drug Reactions (SADRs)

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

Other SAEs

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

Pregnancy Reports

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

AESIs

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to Genentech product) shall be sent within thirty (30) calendar days.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Special Situation Reports

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

Data related to product usage during pregnancy or breastfeeding

Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol

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

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

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.

Exchange of Single Case Reports with Genentech

Dr. Longbrake will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. Completed MedWatch forms as specified in the table below should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

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

All Product Complaints ***without*** an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

- The parties will verify that all single case reports have been adequately received by Genentech via Dr. Longbrake emailing Genentech a Quarterly line-listing documenting single case reports sent by Yale 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 Dr. Longbrake 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.

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.

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

Yale University, as 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.

Yale University, 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.

Yale Center for Clinical Investigation (YCCI) will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Yale University, 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.

YCCI 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:

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32.

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 Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Sponsor 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 within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Sponsor 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 Sponsor 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, 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 Sponsor must also be faxed to Genentech Patient Safety:

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

Email: usds_aereporting-d@gene.com

YCCI will be responsible for the distribution of safety information to Central IRB.

Biomedical Research Alliance of New York Institutional Review Board
1981 Marcus Avenue, Suite 210
Lake Success, NY 11042

For questions related to safety reporting, please contact Genentech 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

Dr. Erin Longbrake will forward a copy of the Final Study Report to Genentech 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

Randomization Codes for Blinded Clinical Trials

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities

QUERIES

Queries related to the Study will be answered by Yale University. However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Yale University 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.

SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Yale, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

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

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

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

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 shall have the final say and control over safety crisis management issues relating to the Product. Yale University agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

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.

STATISTICAL CONSIDERATIONS

Unless otherwise specified, all baseline and efficacy analyses will be based on the intend-to-treat (ITT) population (defined as all randomized patients). The safety evaluable population will include all patients who received any amount of study drug. Unless otherwise specified, all baseline and efficacy analyses will use the ITT population as assigned by randomization. Safety analyses will be performed by treatment received.

The primary analysis will occur when the last randomized patient has reached 4 years and the specified number of new radiological or clinical evidence of MS has accrued as specified in Section 3.1.

All statistical hypotheses for the primary and secondary endpoints and treatment comparisons will tested at the 5% significance level ($\alpha = 0.05$) against two-sided alternatives unless otherwise specified. The SAP will contain full details of the statistical analyses specified for this protocol.

DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation and hypothesis testing regarding the effect of ocrelizumab on the time from baseline to radiological or clinical evidence of MS relative to placebo. P-values, point- and interval estimates of the true underlying hazard ratio will be obtained.

The sample size of this trial is based on testing the null hypothesis of no difference between the control and ocrelizumab arms. This study will enroll approximately 100 patients with an expected recruitment of over 2 years. The sample size of this study is driven by the primary efficacy analysis of radiological or clinical evidence of MS and the following assumptions:

A two-group test of equal times to radiological or clinical evidence of MS

Two-sided type I error = 0.05

33% of the patients in the control arm and 20% of patients in the ocrelizumab arm having radiological or clinical evidence of MS occurring by 4 years.

A final analysis is based on approximately 21 radiological or clinical events to have 80% power 10% annual dropout rate.

SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study and ocrelizumab administration will be summarized. Reasons for premature study discontinuation and treatment discontinuation will be listed and summarized. Major protocol deviations, including violations of inclusion/exclusion criteria will also be listed and summarized.

SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, sex, body mass index), medical history, and neurological examination will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. MS disease history (duration since MS first symptom, duration since MS diagnosis), MS disease status (MS treatment naïve or experienced) will be summarized. The baseline measures of MRI, EDSS, or other important endpoints will also be tabulated. Summaries will be presented overall and by patient cohorts.

EFFICACY ANALYSES

The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment (i.e., the ITT population). All statistical hypotheses for the primary and secondary endpoints and treatment comparisons will be tested at the 5% significance level against two-sided alternative unless otherwise specified.

Primary Efficacy Endpoint

The primary efficacy endpoint for this study is to evaluate the efficacy of ocrelizumab compared with placebo on delaying the time to development of new radiological or clinical evidence of MS, defined as the time from baseline to first new T1 gadolinium-enhancing lesions and/or new or enlarging T2 lesions consistent with MS OR first clinical evidence of MS, i.e., neurological event resulting from CNS demyelination as evidenced by acute or progressive clinical syndrome consistent with MS.

The time to development of radiological or clinical evidence of MS in the ocrelizumab arm and placebo arm will be compared and tested using a stratified log-rank test with the null and alternative hypotheses as follows:

H_0: There is no difference in the time to onset of radiological or clinical evidence of MS between the ocrelizumab and placebo groups.

H_1: There is a difference in the time to onset of radiological or clinical evidence of MS between the ocrelizumab and placebo groups.

The proportion of patients with radiological or clinical evidence of MS over time will be estimated using Kaplan-Meier methodology and the overall hazard ratio will be estimated using a stratified Cox proportional hazards model. In the presence of a large amount of interval censoring, stratified generalized log rank test and stratified proportional hazards model with full likelihood function will be used to compare survival between groups.

Estimands for the Primary Analysis

The primary analysis has a treatment-policy estimand (see ICH E9[R1] 2019) on the basis of the following attributes:

Population: All randomized patients.

Variable: Time from baseline to development of new radiological or clinical evidence of MS.

Intercurrent events:

Withdrawal from treatment: Patients will be followed until the primary analysis regardless of adherence to study treatment or reason for treatment withdrawal. Data will continue to be collected from such patients and included in the analysis, following a treatment-policy strategy.

Initiation of another MS therapy: Data will continue to be collected from such patients and included in the analysis, following a treatment-policy strategy.

Patients still ongoing and without an initial evidence of MS event at the time of study unblinding will be censored at the date of the last assessment.

Population-level-summary estimator: The hazard ratio from a stratified Cox-proportional hazards model will be used. The stratified log-rank p-value will be used to test for statistical significance. Both will be stratified by the factors specified (see Section 4.2.1) for randomization.

Handling of missing data:

Withdrawal from study: a patient will be censored at the time of withdrawal from study.

Missing assessments at scheduled visits prior to last assessment: Missing data at scheduled visits prior to last assessment will not be imputed.

Secondary Efficacy Endpoints

The secondary endpoints for this study are to evaluate the efficacy and impact of ocrelizumab compared with placebo on the basis of the endpoints as described in Section 2.2.1 and biomarkers of disease activity and neuroaxonal damage in peripheral blood.

Each change from baseline for continuous secondary endpoints will be tested and analyzed using a stratified mixed-effects model for repeated measures (MMRM)

assuming missing at random (MAR). Sensitivity analyses will be conducted to assess the validity of this assumption,

For MRI related count endpoints (cumulative number of T2 lesions and T1 gadolinium-enhancing lesions), generalized linear methods appropriate for count data will be used depending on the distribution of the counts, e.g., a stratified negative binomial regression model.

Estimands for the Secondary Analyses

The estimands for the remaining secondary endpoints will have the same population and handling of missing data attributes as for the primary analysis.

Exploratory Efficacy Endpoints

Analyses on exploratory efficacy endpoints will be performed as data allows. Exploratory efficacy endpoints are listed in Section 2.2.2. Further details will be described in the SAP.

SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to CTCAE v5.0 grade. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Associated laboratory parameters, such as hepatic function, renal function, and hematology values, will be grouped and presented together. Marked abnormalities will also be flagged.

BIOMARKER ANALYSES

Biomarkers will be assessed at baseline (screening) and subsequent time points following administration of ocrelizumab or placebo. Biomarkers levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or

predictive properties. Biomarkers may also be analyzed over time as absolute values and/or percent change relative to baseline over time, and may be compared with efficacy, other biomarkers, or safety measurements.

INTERIM ANALYSES

The iDMC will review interim analyses as specified in the iDMC Charter. Interim analyses will be conducted by the unblinded statistician(s) and will focus on recruitment/enrollment, study conduct and safety.

No formal interim analyses for futility or efficacy are planned. However, the aggregate rate of the primary outcome will be monitored throughout the study to assure a sufficient number of events. The following scenario may trigger an interim look for futility.

If we are not on target to reach the hypothesized number of events (in the blinded dataset) by the end of the follow-up period, we will assess whether an extension to follow-up is fiscally feasible. If follow-up is feasible, a non-binding futility analysis using an alpha-spending function will be conducted to determine whether it is worth extending follow-up.

Similarly, we will monitor the current trend of treatment in this patient population. The following scenario may trigger an interim look for efficacy if applicable.

If a new drug is approved, or data supporting the treatment of this patient population is released, we will conduct an interim look for superiority, as long as we have accumulated at least 50% of the information. We will use an alpha-spending function to maintain the overall type I error rate at 0.05.

DATA QUALITY ASSURANCE

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

Study site monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted.

The Sponsor-Investigator-designated monitor conducts monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits and/or remote interim monitoring visits while subjects are on study, and a site close-out visit at the sites. Following each site visit, a visit report will be generated

containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

Protection of the rights, safety and welfare of subjects through review of informed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures

Subject eligibility

Source verification

Protocol compliance

Deviations and Non-compliance

Investigator Site File

GCP compliance

Investigational Drug/ Device Storage and Accountability (including quantity and disposal procedures)

Laboratory Facilities

Equipment maintenance and calibration

Additional study supplies inventory and assessment

Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Sponsor-Investigator and YCCI will define the required study monitoring activities in a Study Monitoring Plan.

INVESTIGATOR REQUIREMENTS

RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years

after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the central IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the central IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

Interim analyses occur as scheduled,

Stopping rules for toxicity and/or response are met,

Risk/benefit ratio is not altered to the detriment of the subjects,

Appropriate internal monitoring of AEs and outcomes is done,

Over-accrual does not occur,

Under-accrual is addressed with appropriate amendments or actions, and

Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

STUDY MEDICATION ACCOUNTABILITY

Each Site Investigator will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug at their site in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the drug depot with the appropriate documentation. The site's method of destroying Genentech-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA, representatives of the Sponsor, and the Central IRB.

ETHICAL CONSIDERATIONS

COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond close of study at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive ocrelizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.6.

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.

INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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 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's Brochure and that are considered possibly or probably related to the ocrelizumab or study drug by the investigator. Some IRBs may have other specific AE requirements to which 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's Brochure, safety amendments and updates, etc.).

CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Sponsor representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

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Appendix 1
Schedule of Activities

	Pre-screening (family members)	Screening [a]	Double-Blind Phase [v]										Unscheduled Visit [b]	Study Completion/ Early Termination [c]
Week	-6	-6	0 Baseline	2	24	48	72	104	130	156	182	208		
Visit Windows (days)	-45-1	-45-1	(-28)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)		
Inclusion/Exclusion Review	x*	x												
Informed consent [d]	x*	x												
Documentation of Disease/Disorder		x												
Demographic data	x*	x												
Medical history and baseline conditions [e]	x*	x												
Lumbar Puncture History		x												
Sleep Status		x			x	x	x	x	x	x	x	x		
Vital signs [f]		x	x	x	x	x	x	x	x	x	x	x	x	x
Weight and Height [g]		x	x	x	x	x	x	x	x	x	x	x	x	x
Complete physical examination [h]		x	x	x	x	x	x	x	x	x	x	x	x	x
EDSS		x	x		x	x	x	x	x	x	x	x	x	x
Neurologic examination [i]		x	x	x	x	x	x	x	x	x	x	x	x	x
Prescreen MRI	x[w]													
MRI brain [p,q]		x			x	x	x	x		x		x	x[r]	x[r]
MRI C-spine [p,q]		x			x	x	x	x		x		x	x[r]	x[r]
Symbol Digit Modality test for cognition	x*		x		x	x	x	x	x	x	x	x	x	x
Neuro QoL	x*		x		x	x	x	x	x	x	x	x	x	x
Assessment of neurologic event			x	x	x	x	x	x	x	x	x	x	x	x
Hematology, chemistry, and urinalysis [j] (Local lab)		x	x	x	x	x		x		x		x	x	x
Pregnancy test [k]		x	x	x	x	x								x
Hepatitis screening		X												
Hepatitis B virus DNA test [l]		x												

	Pre-screening (family members)	Screening [a]	Double-Blind Phase [v]										Unscheduled Visit [b]	Study Completion/ Early Termination [c]
Week	-6	-6	0 Baseline	2	24	48	72	104	130	156	182	208		
Visit Windows (days)	-45-1	-45-1	(-28)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)		
Quantitative Ig (total Ig, IgG, IgM, and IgA) (local lab)		x												
Quantitative Ig (total Ig, IgG, IgM, and IgA) (central lab)			x^x		x	x	x	x	x	x	x	x	x	x
Lumbar puncture/CSF analysis (local lab and biomarkers) [m,p, s]			x^x					x				x	x^r	x^r
Peripheral blood sample for biomarkers [m,s,t]	x		x^x		x	x	x	x	x	x	x	x	x	x
Peripheral blood sample, paired with CSF			x^y					x^y				x^y	X^y	x^y
Serum samples for biomarkers [m,s]	x		x^x		x	x	x	x	x	x	x	x	x	x
Gingival swab for storage	x*		x^x		x	x	x	x	x	x	x	x	x	x
Adverse events [u]		x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications review		x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization IxRS		x												
Methylprednisolone and antihistamine premedication [n]			x	x	x	x								
Ocrelizumab or placebo administration [o]			x	x	x	x								

eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C; MRI = magnetic resonance imaging; MS = multiple sclerosis; NfL = neurofilament light; WGS=Whole genome sequencing; PBMC=peripheral blood mononuclear cells; CSF= cerebrospinal fluid.

Note: (x) indicates that an assessment will only be done if needed.

* If these assessments have been completed during the pre-screening evaluation for an individual who is subsequently found to meet study criteria and enrolled in the main study, they do NOT need to be repeated during the Screening and/or Baseline Visits, as long as those visits take place within 6 weeks of the pre-screening assessment.

[a] The screening window is up to 45 days prior to baseline and all screening and baseline assessments must be conducted prior to first dose.

[b] In the case of a neurological event consistent with CNS demyelination during the study, the patient should have an unscheduled visit and all assessments completed. An MRI may be optionally performed at this visit if clinically indicated. If the patient comes into the clinic for an unscheduled visit for reasons other than relapse, procedures should be performed per standard of care.

[c] In the case of early termination, the patient will be asked to return for an early termination visit/ study discontinuation visit, at which time all assessments must be completed/obtained, except MRI if done within the past 8 weeks, unless clinically indicated.

[d] Written informed consent will be obtained from all patients during screening in order to be eligible.

[e] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. In addition, any previous MS medication should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity.

[f] Vital signs will include measurements of heart rate, systolic and diastolic blood pressure, and temperature. Vital signs should be taken approximately 45 minutes prior to premedication.

[g] After the screening visit, only weight will be measured.

[h] A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited physical examination will be conducted. Any abnormality identified at baseline should be recorded on the eCRF. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

[i] Neurological examinations will be used to distinguish a neurologic event suggestive of MS (i.e., CNS demyelination) from other neurological (non-MS) disorders. Potential neurologic events suggestive of CNS demyelination should be recorded throughout the study period. Investigators will also screen patients for signs and symptoms of worsening neurologic function localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.

[j] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, absolute neutrophil count, and quantitative platelet count. Chemistry will include AST, ALT, total bilirubin, urea or BUN, creatinine, potassium, sodium and calcium. Standard urinalysis will be used to assess kidney function. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during these timepoints.

[k] Serum or urine β-hCG must be performed at screening in women of childbearing potential within 14 days prior to initiation of study drug. Subsequently, urine β-hCG (sensitivity ≥ 25 mIU/mL) must be collected. On infusion visits, the urine pregnancy test should be performed prior to premedication in all women of childbearing potential. If positive, ocrelizumab should be withheld and pregnancy status confirmed with serum β-hCG test.

[l] All patients must have negative HBsAg result and negative HepCAb screening tests prior to study enrollment. If HBcAb is positive at screening, HBV DNA measured by PCR must be negative. For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.

[m] Biomarkers assessed in peripheral blood, CSF, and serum include adaptive and innate immune cell subsets and their soluble factors, RNA, DNA, genetic risk factors (e.g. HLA-DRB1*15:0), and other emerging exploratory markers of disease biology as appropriate. If samples are

collected on the same day as the ocrelizumab infusion, the blood samples should be collected prior to ocrelizumab administration. Blood sample collection may precede ocrelizumab administration by up to 4 weeks. Leftover biological samples will be stored by the central laboratory for later biomarker use. Please refer to the laboratory manual for additional details on laboratory assessments and sample handling.

[n] To be obtained/performed before administration of ocrelizumab (i.e., pre-dose). Premedication with methylprednisolone and antihistamines should be given in accordance to the guidance provided in the USPI.

[o] The first dose of study drug will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, study drug will be administered as a single 600 mg IV infusion at Weeks 24 and 48. A minimum interval of 22 weeks must be maintained between each 600 mg dose of study drug.

[p] LP is required at baseline for subjects who have not previously had CSF analysis or who do not have access to source documentation (including oligoclonal banding testing) for prior CSF analysis. LP is optional at baseline for subjects who have previously had CSF analysis and have appropriate source documentation. LP is always optional at Weeks 104, 208, and unscheduled visits (in case of a clinical neurologic event), at the investigator's discretion. Local lab testing for CSF includes protein, cell count/differential, and oligoclonal banding. CSF oligoclonal banding results must be available prior to randomization and study drug administration. Baseline CSF may be collected up to 4 weeks prior to administration of study drug. If MRI and CSF are performed on the same day, MRI should precede the collection of the CSF specimen and study drug infusion, and the CSF specimen collection should precede the study drug infusion. Blood biomarker samples should be collected as close as possible in time to the CSF sample, which may be prior to study drug administration by up to 4 weeks.

[q] All MRIs will be read by a central reading center. Prior to initiation of study drug a QC report for the Screening MRI scan must have been received from the centralized reading center confirming scan passed QC. The brain MRI requires at least 2 business days from scan receipt to be quality checked before dosing of study drug. Screening MRIs must also be confirmed by the central MRI reader to meet 2017 McDonald criteria for dissemination in space prior to patient randomization. Contrast agent (gadolinium) required only at screening MRI and annually (Weeks 48, 104, 156, and 208).

[r] To be obtained/performed optionally, at the Investigators discretion, in case of neurologic event or suspected neurologic event suggestive of MS.

[s] Biological samples may be sent to central laboratory, local laboratory or other academic laboratory and specialized sites for final processing, analysis and reporting due to cell viability and biomarker recovery, such as but not limited to B cell, T cell and innate immune cell subset samples in CSF. Please refer to laboratory manual for details.

[t] A PD DNA sample will be collected for patient genotyping (whole genome sequencing; WGS) at the Baseline visit. If the DNA sample is not collected at the baseline visit, it may be collected at any subsequent visit. Collection and submission of this sample is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, collection of this sample will not be applicable at that site.

[u] Adverse events will be reported throughout the study.

[v] The primary analysis for this study is event driven, therefore the study duration in the double-blind phase will vary for each patient. In the event that the requisite number of events have accumulated study-wide before the minimum 3-year follow-up, patients will then be unblinded and followed for a minimum of 3 years.

[w] Pre-screening MRI scans must include FLAIR sequences to establish whether the individual meets 2017 McDonald criteria for DIS. Pre-screening MRIs will be interpreted by site PIs to determine whether they meet 2017 McDonald criteria for dissemination in space. Individuals established to have RIS in this way must subsequently undergo a full, screening MRI as noted elsewhere.
[x] Baseline blood, gingival swab and CSF samples may be collected up to 4 weeks prior to administration of study drug, but should be performed after successful completion of screening activities. Results for CSF oligoclonal banding must be available prior to randomization.
[y] Blood collection for biomarkers (either 10X sequencing or storage) should always be paired with any CSF collection. If a subject has declined optional LPs, this blood biomarker collection would not take place at those timepoints.

Appendix 2
Immune Cell Network Sub-study

RATIONALE

Single-cell transcriptomic techniques, such as single-cell RNA sequencing (scRNAseq), have been utilized in MS to identify cellular heterogeneity across multilineage populations to better understand the molecular and cellular processes that contribute to the pathogenesis of disease. Thus, single-cell transcriptomics have the potential utility to identify biomarkers that enable the identification of risk factors for MS onset and subsequent disease progression. As such, comprehensive findings derived from integrated single cell analysis of blood and CSF in MS patients have revealed compartment specific profiles based on cellular composition and transcriptional phenotypes. The immunologic and transcriptional shifts that accompany the evolution from RIS to clinical MS are unknown. Herein, we propose to identify biomarkers that characterize the emergence of MS among RIS patients by using single cell transcriptomics in blood and CSF.

PRIMARY OBJECTIVES

To identify compartment-specific changes in immune cell population frequency and phenotype in blood and CSF at single-cell resolution using scRNAseq to better understand the (1) immunological shifts accompanying clinical conversion from RIS to clinical MS, (2) dynamics and characteristics of B cell reconstitution and (3) clinical response to B cell depletion in RIS patients treated with ocrelizumab or placebo, if feasible.

SECONDARY OBJECTIVE

To longitudinally characterize the dynamic changes in B cell and T cell repertoire, as well as frequency and phenotype of myelin-reactive T cells in RIS patients treated with ocrelizumab or placebo, by comparing those who convert to MS with those who do not.

EXPLORATORY OBJECTIVE

To longitudinally characterize the dynamic compartment-specific changes in frequency and phenotype of myelin-reactive T cells in RIS patients treated with ocrelizumab or placebo.

Primary Endpoints

Change from Baseline to Weeks 104 and 208 in matched peripheral blood and CSF immune cell frequency and phenotype as detected by scRNAseq

Change from Baseline to Weeks 104 and 208 in CSF immune cell frequency and phenotype as detected by scRNAseq

Secondary Endpoints

Change from Baseline to Weeks 104 and 208 in peripheral blood B cell receptor repertoire

Change from Baseline to Weeks 104, and 208 in CSF B cell receptor repertoire

Change from Baseline to Weeks 104 and 208 in peripheral blood T cell receptor repertoire

Change from Baseline to Weeks 104 and 208 in CSF T cell receptor repertoire

Correlation between changes in compartment-specific immune repertoire and radiologic/clinical outcomes.

Exploratory Endpoints

Change from Baseline to Weeks 104 and 208 in frequency and immunophenotype of myelin specific CD4+ T cells in peripheral blood as detected by myelin:MHC II tetramers

Change from Baseline to Weeks 104 and 208 in frequency and immunophenotype of myelin specific CD4+ T cells in CSF as detected by myelin:MHC II tetramers

Change from Baseline to Weeks 104 and 208 in frequency and immunophenotype of myelin specific CD8+ T cells in peripheral blood as detected by myelin:MHC I tetramers

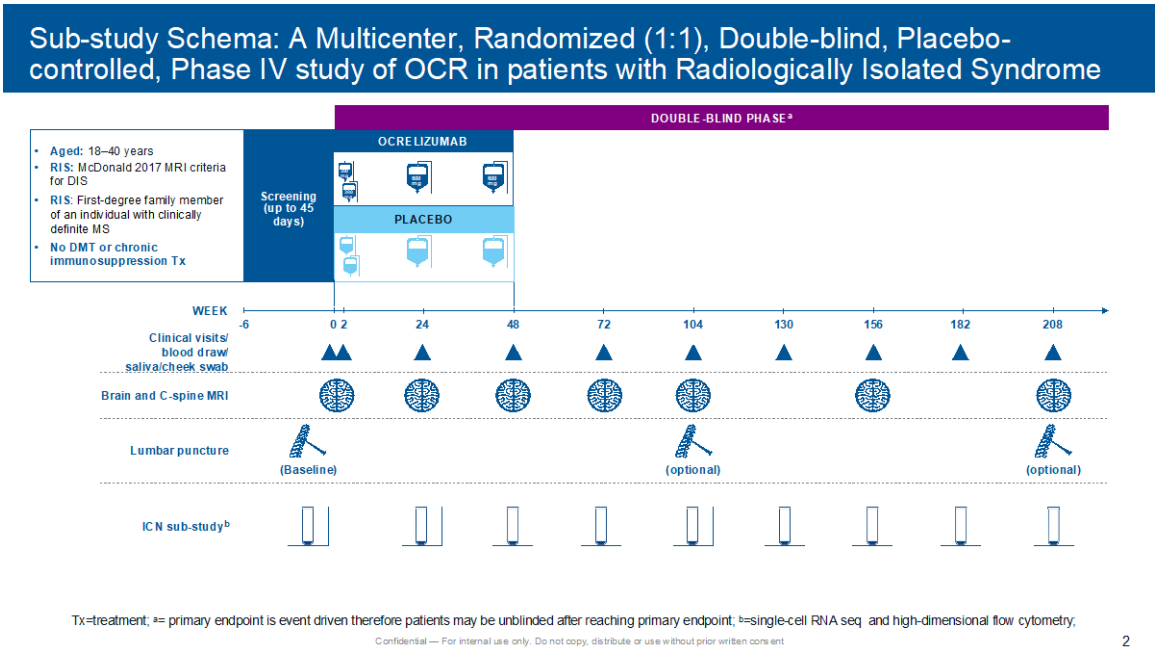
Change from Baseline to Weeks 104 and 208 in frequency and immunophenotype of myelin specific CD8+ T cells in CSF as detected by myelin:MHC I tetramers

Correlation between changes in compartment-specific myelin-reactive T cell composition and phenotype with radiologic/clinical outcomes.

SAMPLE SIZE

Given the exploratory nature of this sub-study, there is insufficient data available in RIS patients to reasonably and accurately perform power calculations. Previous studies in MS have detected significant differences in small cohorts ranging from 8–21 patients. Therefore, this sub-study will enroll approximately 20 patients to be recruited from 5–10 study centers. Baseline samples will be collected from all sub-study participants. Longitudinal samples will be obtained only from sub-study participants who consent to one or more additional lumbar punctures. For these participants, paired blood and CSF will be also be collected at weeks 104 and 208 (participants may consent to one or both optional LPs) for use in advanced immunologic assays as detailed above.

Appendix 3
Sub-study Schema



Appendix 4
Registry of First Degree Family Members with MS

RATIONALE

The pathophysiological processes occurring in MS are believed to occur long before the clinical manifestation of MS onset; however, limited information exists that characterizes this prodromal phase. It has been reported that there is increased utilization of health care in the years leading up to the clinical recognition of MS. First degree relatives of those living with MS are at increased risk for RIS and MS, with an estimated 3%–10% of clinically unaffected siblings having lesions highly suggestive of demyelination. In identical twins this risk is even greater. If one twin has MS the risk for the other developing MS is approximately 25%–30%. The natural history of these individuals is poorly understood.

This registry will follow first-degree relatives of those patients with MS, that do not meet RIS MRI criteria at screening over the course of the approximately a 6 year total study duration (i.e., total study length including screening to end of study) in order to better understand the natural history of those who are at high-risk of developing MS and to gain insight into the earliest pre-clinical and/or prodromal manifestations of disease. Annual phone check-ins over the course of the total study duration will assess general health (Neuro-QoL™), including clinically significant diseases, neurologic and autoimmune diagnosis, symptoms, all medications (i.e., prescription, over-the-counter, herbal or homeopathic remedies, supplements), number of emergency department visits, hospitalizations, office visits/physician encounters (i.e., specialists), etc. In the event of a MS diagnosis, any MS medication should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Findings derived from this registry may ultimately allow for earlier identification of MS by implementing into diagnostic procedures.

Schedule of Assessments for Registry						
			Week			
	Pre-screening	To main study if meets criteria If MRI does not qualify for main study, then to registry	48 (phone)	104 (phone)	156 (phone)	208 (phone)
ICF	X					
Demographic Data	X					
Medical history & baseline conditions	X					
MRI brain (only FLAIR sequence required)	X					
Symbol Digit Modality Test	X					
Peripheral blood sample for DNA and biomarkers	X					
Gingival swab for storage	X					
NeuroQOL	X		X	X	X	X

Updated health/ medication history			X	X	X	X

Exploratory Endpoint:

Change from Baseline to Weeks 48, 104, 156 and 208 in general health (Neuro-QoL™), including clinically significant diseases, neurologic and autoimmune diagnosis, symptoms, all medications (i.e., prescription, over-the-counter, herbal or homeopathic remedies, supplements), number of emergency department visits, hospitalizations, and office visits/physician encounters (i.e., specialists), etc., as assessed by phone check-in

Appendix 5

Expanded Disability Status Scale

Kurtzke Expanded Disability Status Scale (EDSS)

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

❑ 10.0 - Death due to MS.

---

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Source: http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab

Appendix 6
New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 7
Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if PML Is Suspected

If the clinical presentation is suggestive of progressive multifocal leukoencephalopathy (PML) (see Table1), further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (Berger et al. 2013; see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) should be undertaken for the detection of JC virus (JCV) DNA by polymerase chain reaction using a validated sensitive assay. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF. This sample will be stored for 1 year after the last patient, last visit.

There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

MRI Assessment

Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a brain MRI scan that includes fluid-attenuated inversion recovery and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive of PML (see Figure 1).

Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 2 in Appendix 7) for differences in lesion characteristics that may help differentiate between PML and MS.

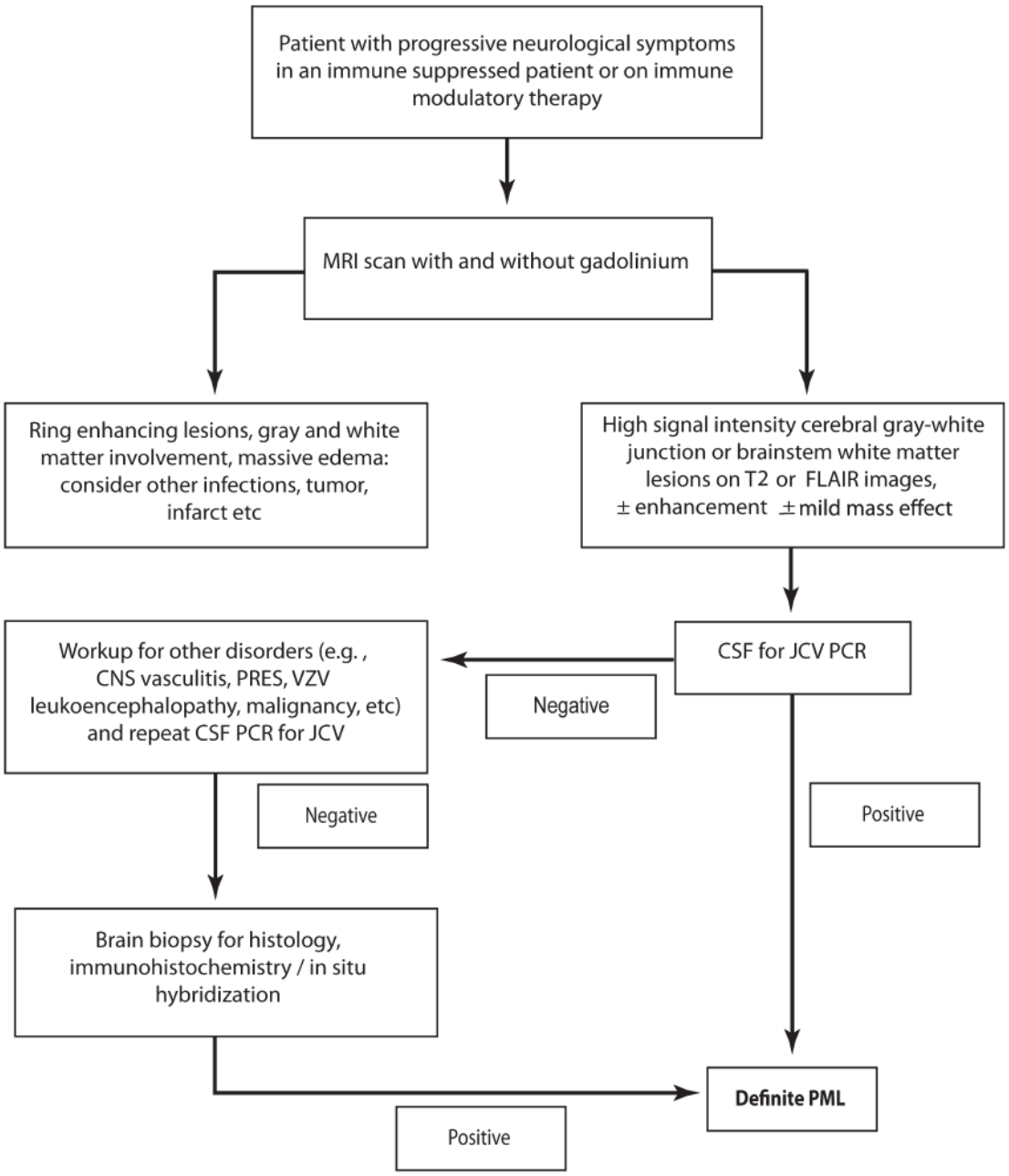
CSF Assessment

The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.

If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.

If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Figure 1 Diagnostic Algorithm Framework for PML (Berger et al. 2013)



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

Table 1 Clinical Signs and Symptoms Typical of MS and PML

Clinical Signs and Symptoms Typical of MS and PML*		
	MS	PML
Onset	**Acute**	**Subacute**
Evolution	➢ Over hours to days ➢ Normally stabilized ➢ Resolve spontaneously even without therapy	➢ Over weeks ➢ Progressive
Clinical presentation	➢ Diplopia ➢ Paresthesia ➢ Paraparesis ➢ Optic neuritis ➢ Myelopathy	➢ Cortical symptoms/signs ➢ Behavioral and neuropsychological alteration ➢ Retrochiasmal visual defects ➢ Hemiparesis ➢ Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Adapted from Kappos et al. 2007.

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	Multiple Sclerosis	PML
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging;
PML = progressive multifocal leukoencephalopathy.
Adapted from Yousry et al. 2006.

REFERENCES

Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology 2013;80:1430–8.

Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol 2007;6:431–41.

Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924–33.

Appendix 8
2017 Revised McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical Attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
⩾2	⩾2	None
⩾2	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None
⩾2	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1	⩾2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI ‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands

Appendix 9
Pregnancy Outcome and Infant Health Information on First Year of Life

Pregnancy Outcome and Infant Health Information on First Year of Life

If twin or multi-gestational pregnancy, this questionnaire has to be filled out separately for each baby born in the multi-gestational pregnancy.

Please check all that apply and provide detailed information on complications in infant on last page.

Table 1: Parent's (or person with parental responsibility in law) consent to data collection

Has parent's (or person's with parental responsibility in law) data authorization form been signed?	☐Yes ☐No	Date signed _____	Other – comment _____
	Date consent withdrawn: (if applicable)		

Table 2: Information on birth

Mode of birth	☐Vaginal delivery Forceps / vacuum: - Yes ☐ - No ☐ ☐Cesarean section (CS) - scheduled CS ☐ - emergency CS ☐	Reason for assisted delivery/Cesarean section_____
Gestational age at birth	_____ weeks - since conception ☐ - since LMP ☐	Induced labor - Yes ☐ - No ☐

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐Small for gestational age (SGA) ☐Low birth weight ☐Short birth length	If Growth alteration present: Specify weight:_____ Specify length: _____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____	
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____	
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____	
Functional deficit (except for infections, which should be described in separate table below) - Yes ☐ - No ☐	☐Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

Status of infant at the time of latest follow-up (at birth, 3 months, 6 months, 12 months)

Table 4: Status of infant

Date of Assessment		Contributing factors/ Comments
Status of infant	☐Normal ☐Abnormal, specify abnormality: _____ ☐Neonatal/infant death, specify cause and date of death: _____	_____ _____
Nursing status	☐Exclusive breastfeeding ☐Mixed feeding (partial breastfeeding along with infant formula and/or baby food), specify date since when: _____ ☐Fully weaned, specify date since when: _____	_____

Infections in neonate and infant during first year of life

Any infection detected at birth?

Yes ☐
No ☐
Unknown ☐

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.

If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.

If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on infection in neonate at birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify): _____		**Outcome of infection?**	**Duration of infection?**
		☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration**:_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No	☐Yes, specify: _____ ☐No
☐Life-threatening (Grade 4) ☐Death (Grade 5)		☐Unknown	☐Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 6: Maternal risk factors for neonatal infection (during most recent pregnancy, if infant developed neonatal infection at birth)

Maternal risk factors for neonatal infection	**Date of diagnosis**	If **diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
☐Maternal intrapartum colonization or infection with group B streptococcus (GBS) ☐Maternal listeriosis ☐Premature rupture of membranes (PROM) ☐Meconium in amniotic fluid (meconium-stained liquid) ☐Active genital herpes infection ☐CMV ☐HPV (papilloma virus) Other, specify	_____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify: (e.g., any specific antibodies and their titers)	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Any infection detected during first year of infant's life?

Yes ☐
No ☐
Unknown ☐

If infection detected during first year of infant's life, then Table 7 should to be filled out and additional detailed information may be provided on last page. If no infection developed during first 12 months of life, then please move directly to Table 8.

Table 7: Information on infection detected during first year of infant's life

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____ _____	**Age:**_____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti- infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Table 8: Vaccinations administered to infant at birth and during first year of age

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐Hemophilus influenza type b			
☐Pneumococcal			
☐Poliovirus ☐Attenuated oral polio vaccine ☐Inactivated polio vaccine			
☐Meningococcal group B bacteria			
☐Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
☐Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

Fetal/neonatal abnormalities (in previous pregnancies)			Please, provide specifics including contributing factors
None ☐	Yes ☐	Unknown ☐	
Infection; if yes, specify			
Death in utero; if yes, specify reason			
Birth defects; if yes, specify			
Family history of birth defects; if yes, specify			
Small for gestational age at birth (or Intrauterine growth retardation)			
Premature delivery (before 37 weeks)			
Other; specify			

Detailed information on health-related findings in infant during first year of life

Please enter text in the free text box below.

Appendix 10

Neuro-QOL

Anxiety – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
EDANX53	I felt uneasy……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX48	Many situations made me worry……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX55	I had difficulty calming down…..……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX18	I had sudden feelings of panic……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQANX07	I felt nervous when my normal routine was disturbed…….…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Depression – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
EDDEP29	I felt depressed……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP09	I felt that nothing could cheer me up……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP48	I felt that my life was empty……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP04	I felt worthless……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP39	I felt I had no reason for living……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP45	I felt that nothing was interesting……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fatigue – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG11	I felt that I had no energy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG15	I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG06	I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG07	I was too tired to leave the house……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG14	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG02	I had to limit my social activity because I was tired…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Cognition Function– Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely (once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
NQCOG64r1	I had to read something several times to understand it……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG75r1	My thinking was slow……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG77r1	I had to work really hard to pay attention or I would make a mistake…….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG80r1	I had trouble concentrating…….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	How much DIFFICULTY do you currently have…	None	A little	Somewhat	A lot	Cannot do
NQCOG22r1	reading and following complex instructions (e.g., directions for a new medication)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG24r1	planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG25r1	managing your time to do most of your daily activities?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG40r1	learning new tasks or instructions?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Emotional and Behavioral Dyscontrol – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
EDANG42	I had trouble controlling my temper……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER05	It was hard to control my behavior…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER06	I said or did things without thinking……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER07	I got impatient with other people……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER11	I was irritable around other people…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER12	I was bothered by little things……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER17	I became easily upset……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER19	I was in conflict with others……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Positive Affect and Well-Being - Short Form

Please respond to each question or statement by marking one box per row.

	Lately…	Never	Rarely	Sometimes	Often	Always
NQPPF14	I had a sense of well-being…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF12	I felt hopeful……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF15	My life was satisfying……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF20	My life had purpose……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF17	My life had meaning……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF22	I felt cheerful……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF19	My life was worth living……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF16	I had a sense of balance in my life…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPPF07	Many areas of my life were interesting to me……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQPRF01	I can keep up with my family responsibilities……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF03	I am able to do all of my regular family activities…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF08	I am able to socialize with my friends…...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF09	I am able to do all of my regular activities with friends…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF17	I can keep up with my social commitments……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF26	I am able to participate in leisure activities…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF32	I am able to perform my daily routines…..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPRF34	I can keep up with my work responsibilities (include work at home)….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Satisfaction with Social Roles and Activities – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
NQSAT 03	I am bothered by my limitations in regular family activities	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT 23	I am disappointed in my ability to socialize with my family……..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT14	I am bothered by limitations in my regular activities with friends.……	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQSAT11	I am disappointed in my ability to meet the needs of my friends	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
NQSAT33	I am satisfied with my ability to do things for fun outside my home…….....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSAT32	I am satisfied with the amount of time I spend doing leisure activities…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSAT47	I am satisfied with how much of my work I can do (include work at home).……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSAT 46	I am satisfied with my ability to do household chores or tasks…….....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Communication – Short Form

Please respond to each question or statement by marking one box per row.

How much DIFFICULTY do you currently have…

		None		A little	Somewhat	A lot	Cannot do
NQCOG01	writing notes to yourself, such as appointments or 'to do' lists?.....	☐ 5		☐ 4	☐ 3	☐ 2	☐ 1
NQCOG04	understanding family and friends on the phone?.....	☐ 5		☐ 4	☐ 3	☐ 2	☐ 1
NQCOG08	carrying on a conversation with a small group of familiar people (e.g., family or a few friends)?.....	☐ 5		☐ 4	☐ 3	☐ 2	☐ 1
NQCOG10	organizing what you want to say?.....	☐ 5		☐ 4	☐ 3	☐ 2	☐ 1
NQCOG11	speaking clearly enough to use the telephone?.....	☐ 5		☐ 4	☐ 3	☐ 2	☐ 1

Upper Extremity Function (Fine Motor, ADL) – Short Form

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA40	Are you able to turn a key in a lock?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA50	Are you able to brush your teeth?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX44	Are you able to make a phone call using a touch tone key-pad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB21	Are you able to pick up coins from a table top?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA43	Are you able to write with a pen or pencil?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA35	Are you able to open and close a zipper?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Lower Extremity Function (Mobility) – Short Form

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFC45	Are you able to get on and off the toilet? ...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA30	Are you able to step up and down curbs?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to get in and out of a car?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA45	Are you able to get out of bed into a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA12	Are you able to push open a heavy door? ..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA31	Are you able to get up off the floor from lying on your back without help?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Sleep Disturbance – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQSLP02	I had to force myself to get up in the morning……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP03	I had trouble stopping my thoughts at bedtime……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP04	I was sleepy during the daytime…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP05	I had trouble sleeping because of bad dreams……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP07	I had trouble falling asleep…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP12	Pain woke me up……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP13	I avoided or cancelled activities with my friends because I was tired from having a bad night's sleep…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQSLP18	I felt physically tense during the middle of the night or early morning hours……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 11 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (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 Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET