Official Title: **AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**

NCT Number: NCT02637856

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PROTOCOL

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MN30035
VERSION NUMBER:	5
EUDRACT NUMBER:	Not applicable
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 4 December 2015
DATES AMENDED:	Version 2: 4 March 2016 Version 3: 12 December 2016 Version 4: 19 October 2017 Version 5: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	[redacted]	19-Jun-2018 09:04:49

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol MN30035 was amended primarily to include an optional shorter infusion substudy. In this substudy, eligible patients enrolled in the main study will have the option to receive a dose of 600-mg ocrelizumab at Week 96 infused over a shorter time period than the approved administration rate. The current FDA-approved Ocrevus® (ocrelizumab) labeling recommends that the 600-mg ocrelizumab dose be infused at a maximum rate of 200 mL per hour for a duration of 3.5 hours or longer. Administration of ocrelizumab over a shorter infusion time would help convenience of use and compliance for both patients and healthcare practices (Sections 1.4, 3.4, and 3.6; and Appendix 2).

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- Because ocrelizumab is now approved by the FDA, the Safety Follow-up Period in the main study has been shortened throughout the protocol from 24 and 48 weeks after the last dose of ocrelizumab in the study to only 24 weeks after the last dose. Thus, the main study will not exceed 96 weeks in duration. Additionally, B-cell monitoring has been removed throughout the protocol.
- Birth control requirements for women in the study have been revised to include certain “acceptable” forms of birth control, as “highly effective” birth control methods, which are more stringent, are no longer required (Section 4.1.1).
- Premedication information for methylprednisolone (or equivalent steroid) has been revised to remove the need for slow infusion over approximately 15 minutes, in order to align with the global ocrelizumab program (Section 4.3.2.1, Section 4.3.3, and Appendix 1).
- Safety language has been added to the protocol to indicate that women who accidentally become pregnant during the study will no longer be required to permanently discontinue ocrelizumab infusions. Given that there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, ocrelizumab infusions are not permitted while a patient is pregnant or breastfeeding. However, patients may now resume infusions following a thorough benefit–risk discussion with their investigator after the patient’s pregnancy and breastfeeding are finished. Patients who have already permanently discontinued from the study because of pregnancy (or for any other reason) may not be re-enrolled in the study (Sections 4.6.2, 4.6.3, and 5.4.3.1).
- Information has been updated on risks associated with ocrelizumab (Section 5.1.3).
- The Medical Monitor has been changed to [redacted], M.D., Ph.D. (Section 5.4.1).
- To further strengthen safety monitoring for special situations that may or may not result in an adverse event, instructions have been added regarding the reporting of

medication errors and accidental overdose (Section 5.4.4) and the prior, less specific text on the topic has been deleted (Section 5.3.5.12).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
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TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE HAD A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MN30035
VERSION NUMBER:	5
EUDRACT NUMBER:	Not applicable
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the effectiveness of ocrelizumab 600 mg intravenously (IV) every 24 weeks over 96 weeks in patients with relapsing remitting multiple sclerosis (RRMS) who have had a suboptimal response to an adequate course of a disease-modifying treatment (DMT).

A suboptimal response is defined by having one or more clinically reported relapse(s), OR one or more T1 gadolinium (Gd)-enhanced lesion(s), OR two or more new or enlarging T2 lesions on magnetic resonance image (MRI) despite being on a stable dose of the same DMT for at least 6 months. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT.

Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks in patients with RRMS who have had a suboptimal response to an adequate course of a DMT as measured by the nature and incidence of adverse events.

Exploratory Objective

The exploratory objective of this study is to further assess the effectiveness of ocrelizumab by monitoring patient-reported outcomes (PROs) related to quality of life and treatment satisfaction.

Study Design

Description of the Study

This study is a prospective, multicenter, open-label, effectiveness, and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. This study will be conducted in North America. An adequate course of prior DMT is defined as the same DMT administered for at least 6 months. Ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.

Patients will be assessed for effectiveness and safety every 24 weeks. The study will consist of the following periods, described in detail below:

- Screening Period: Up to 4 weeks
- Treatment Period: Open-label treatment period of *72* weeks (4 doses)
- Safety Follow-up Period: Observation *24* weeks after the last infusion of study drug for patients who discontinue or who chose not to continue with commercially available ocrelizumab at the end of study

Eligible patients may choose to participate in an optional shorter infusion substudy at the Week 96 visit, during which they will receive ocrelizumab infused over a shorter time period than the approved administration rate (Appendix 2).

Number of Patients

This study will enroll approximately 600 patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a definite diagnosis of multiple sclerosis (MS), confirmed per the revised 2010 McDonald criteria (Polman et al. 2011; Appendix 4), and have the relapsing remitting form of MS
- Have a length of disease duration, from first symptom, of ≤ 12 years
- Have been treated with an adequate course of treatment with no more than three prior DMTs
  - Adequate treatment is defined as ≥ 6 months on a DMT.
  - Discontinuation of the most recent adequately used DMT must have been due to suboptimal response as defined below.
- Suboptimal response while on his/her last adequately used DMT (for ≥ 6 months); a suboptimal response is defined by having one of the following qualifying events despite being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new or enlarging T2 lesions on MRI

  These qualifying events must have occurred while on the last adequately used DMT. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT from the date of screening.
- Expanded Disability Status Scale (EDSS) of 0 to 5.5, inclusive, at screening
- For women of childbearing potential: agreement *to use an acceptable birth control method:*
  - *Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action*
  - *Male or female condom with or without spermicide*
  - *Cap, diaphragm, or sponge with spermicide*
  - *A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods are also considered acceptable, but not highly effective, birth control methods)*

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of primary progressive multiple sclerosis (PPMS), progressive relapsing multiple sclerosis (PRMS), or secondary progressive multiple sclerosis (SPMS)
- Inability to complete an MRI (contraindications for MRI include but are not restricted to claustrophobia, weight, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gd-enhancing ligands, etc.).
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of central nervous system (CNS) or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - History of progressive multifocal leukoencephalopathy (PML)
- Pregnancy or lactation, or intention to become pregnant during the study
  - Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to initiation of study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, and gastrointestinal or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] Class III/IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease but excluding fungal infection of nail beds) or any severe 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
- History of or currently active primary or secondary immunodeficiency
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)
- History of recurrent aspiration pneumonia requiring antibiotic therapy

- History of malignancy, including solid tumors and hematological malignancies, except basal cell, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been excised with clear margins
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of coagulation disorders
- History of alcohol or drug abuse within 24 weeks prior to screening
- Previous treatment with natalizumab within 12 months prior to screening unless failure was due to confirmed, persistent anti-drug antibodies
  - Patients previously treated with natalizumab will be eligible for this study only if duration of treatment with natalizumab was < 1 year and natalizumab was not used in the 12 months prior to screening. Anti-JCV antibody status (positive or negative) and titer (both assessed within the year of screening) must be documented prior to enrollment. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay (e.g., ELISA).
- Previous treatment with systemic cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate
- Treatment with IV immunoglobulin within 12 weeks prior to baseline
- Treatment with dalfampridine (Ampyra®) unless on stable dose for $\geq$ 30 days prior to screening
  - Wherever possible, patients should remain on stable doses throughout the treatment period.
- Receipt of a live vaccine within 6 weeks prior to baseline; in rare cases when patient requires vaccination with a live vaccine, the screening period may need to be extended but cannot exceed 8 weeks
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.
  - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- Previous treatment with fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) in patients whose lymphocyte count is below the lower limit of normal (LLN)
- Contraindications to or intolerance of oral or IV corticosteroids, including IV methylprednisolone (or equivalent steroid) administered according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents preceding
- Treatment with alemtuzumab (Lemtrada®)
- Treatment with a B-cell targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental (Exception: treatment with an experimental drug that was subsequently approved in the patient's country is allowed.)
- Laboratory test results as follows:
  - Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)
  - Lymphocyte count below LLN
  - CD4 count $< 300/\mu L$
  - AST or ALT $\geq 3.0 \times$ the upper limit of normal (ULN)

- Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
- Total neutrophil count below LLN

Re-testing before baseline: in rare cases in which the screening laboratory samples are rejected by the laboratory (e.g., hemolyzed sample) or the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated. Any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before enrollment must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.

End of Study

The end of the treatment period is defined as the date when the last patient, last visit (LPLV) at 96 weeks occurs *(or at Week 100 in the substudy)*.

Length of Study

The total length of the *study* is expected to be approximately 4 years from the first patient enrolled to LPLV.

The end of study is defined as the LPLV of the safety follow-up.

Investigational Medicinal Products

Test Product (Investigational Drug)

Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks, for a maximum of 4 doses.

Non-Investigational Medicinal Products

Premedicate with 100-mg methylprednisolone (or equivalent) completed approximately 30 minutes prior to each ocrelizumab infusion and with an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs).

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered to further reduce the frequency and severity of IRRs.

Statistical Methods

Primary Efficacy Outcome Measures

The primary efficacy assessment will be the proportion of patients who are free of any protocol-defined events during a 96-week period. The definition of a protocol-defined event is the occurrence of at least one of the following while on treatment with ocrelizumab:

- A protocol-defined relapse
- A T1 Gd-enhanced lesion on brain MRI
- A new and/or enlarging T2 lesion on brain MRI
- Confirmed disability progression (24 weeks)

Determination of Sample Size

Assuming a) the expected proportion of patients who will be event free during 96 weeks is 45%; b) the type one error rate is 5% and the half-width of 95% confidence interval (CI) for the proportion is 4%; c) the probability that half-width of 95% CI is at most 4% is 80%, then the required sample size will be $n = 600$.

Interim Analyses

It is estimated that two to three interim analyses will be performed during the course of the study, according to patient enrollment and availability of data of interest. Interim analyses may be used for internal decision making, hypothesis generation, abstraction/publication for major MS conferences, or other purposes, as applicable. Details on the timing and scope of interim analyses will be described in the Statistical Analysis Plan.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
ADR	adverse drug reaction
ARR	annual relapse rate
β-hCG	beta subunit human chorionic gonadotropin
CDP	confirmed disability progression
CI	confidence interval
CNS	central nervous system
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMT	disease-modifying treatment
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion-recovery
FSS	Functional Systems Score
GA	glatiramer acetate
Gd	gadolinium
HAM	HTLV-1 associated myelopathy
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HepCAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HTLV-1	human T-lymphotropic virus 1
ICH	International Council on Harmonisation
IFN-β	interferon beta
IMP	investigational medicinal product
IRR	infusion-related reaction
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice/Web response system
KLH	keyhole limpet haemocyanin
LDH	lactate dehydrogenase

Abbreviation	Definition
LLN	lower limit of normal
LPLV	last patient, last visit
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
MMRM	mixed model with repeated measure
MRI	magnetic resonance image
MS	multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale (29-item scale)
NCI	National Cancer Institute
NEDA	no evidence of disease activity
NK	natural killer
NYHA	New York Heart Association
PCR	polymerase chain reaction
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PPMS	primary progressive multiple sclerosis
PRMS	progressive relapsing multiple sclerosis
PRO	patient-reported outcome
PY	patient years
QOL	quality of life
RA	rheumatoid arthritis
RMS	relapsing multiple sclerosis
RR	relative reduction
RRMS	relapsing remitting multiple sclerosis
SAP	statistical analysis plan
SD	standard deviation
SPMS	secondary progressive multiple sclerosis
TB	tuberculosis
ULN	upper limit of normal
U.S.	United States
USP	United States Pharmacopeia

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3 million worldwide (National Multiple Sclerosis Society). MS primarily affects young adults, with 70% – 80% of patients having an age of onset (i.e., initial clinical presentation to a physician) between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002), and has a strong gender bias, with approximately 64% – 70% of diagnosed patients being women (Goodin 2014).

MS is clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression. These include relapsing remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) (Lublin et al. 1996). Accumulated disability is the fate of most patients with MS when a 20- to 25-year perspective is considered (Trojano et al. 2003).

Approximately 85% of MS patients initially present with RRMS (Confavreaux et al. 2000; Leray et al. 2015). The majority of RRMS patients will transition into SPMS within 20 – 25 years (Trojano et al. 2003).

Over the past two decades, there has been a substantial increase in the number and type of available treatments for RRMS. Yet, despite suboptimal response to an adequate course of treatment with a disease-modifying treatment (DMT), defined as the same DMT administered for at least 6 months, a significant proportion of treated patients with RRMS will show signs of disease activity. Suboptimal responses, defined in this protocol as one or more clinically reported relapse(s), one or more T1 gadolinium (Gd)-enhanced lesion(s), OR two or more new or enlarging T2 lesions on brain magnetic resonance imaging (MRI) despite being on a stable dose of the same DMT for at least 6 months, are reported in approximately one-third of patients receiving interferon beta (IFN-β) therapy (Bergvall et al. 2014; Durelli et al. 2008; Fernández et al. 2005; Waubant et al. 2003). Disease activity while receiving a DMT is associated with poorer long-term outcomes (Bermel et al. 2013), thus subsequent treatment with a more effective therapy may be warranted in patients with breakthrough signs and symptoms. Consequently, reported rates of treatment switching for suboptimal responses range from 20% – 35% of patients (Rio et al. 2012; Gajofatto et al. 2009; Teter et al. 2014).

While clinical experience and retrospective studies suggest that better disease control is obtained by escalating to a higher-efficacy therapy, few prospective studies have been conducted. A prospective, observational study evaluated the outcomes of patients who failed first-line treatment with IFN-β or glatiramer acetate (GA) who were subsequently treated with a different IFN-β formulation or GA or were escalated to natalizumab (Prosperini et al. 2012). At 1 year, no significant differences in disease activity were

observed between the two groups. However, after 2 years, significantly greater proportions of patients escalated to natalizumab were free from relapse, disability progression, MRI activity, and combined activity than patients who were treated with IFN-β or GA. In the Phase III trial (CARE-MS II) published by Coles and colleagues, patients who had one or more relapses while receiving IFN-β or GA therapy were randomized to receive either IFN-β or alemtuzumab. Significant reductions in relapse rates and the accumulation of disabilities were reported with alemtuzumab compared to IFN-β at 1 year (Coles et al. 2012). However, more data from large-scale, prospective studies assessing patients who are subsequently treated with higher-efficacy therapies following suboptimal control with first-line treatment are needed.

A Phase II study provided initial evidence that ocrelizumab could be effective at further reducing MS disease activity (i.e., annual relapse rate [ARR] and MRI activity) following initial IFN-β therapy. Additional data are also available on previously treated patients in two completed Phase III studies (Studies WA21092 [OPERA I] and WA21093 [OPERA II]), but only in a subgroup of patients. Therefore, this prospective study was designed to specifically evaluate the effectiveness and safety of using ocrelizumab in patients who show a suboptimal response to an adequate course of a DMT.

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B cells (Klein et al. 2013), which are believed to play a critical role in MS.

CD20 is a cell surface antigen found on pre-B cells, mature B cells, and memory B cells, but it is not expressed on lymphoid stem cells and plasma cells (Stashenko et al. 1980; Loken et al. 1987; Tedder and Engel 1994). While ocrelizumab selectively depletes CD20-expressing B cells (Kappos et al. 2011), the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved (Martin and Chan 2006; DiLillo et al. 2008). In addition, innate immunity and total T-cell numbers are not affected (WA21493 Clinical Study Report).

See the Ocrelizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.2.1 Summary of Clinical Studies of Ocrelizumab in Multiple Sclerosis

1.2.1.1 Clinical Studies

Current studies of ocrelizumab include four ongoing controlled clinical trials in patients with MS: three Phase III studies (pivotal Studies WA21092 and WA21093 and Study WA25046) and one Phase II study (Study WA21493).

Studies WA21092 and WA21093 are multicenter, randomized, parallel-group, double-blind, double-dummy, active-comparator studies of ocrelizumab in patients with

relapsing multiple sclerosis (RMS). Patients receive 600 mg intravenous (IV) ocrelizumab every 24 weeks or 44 μg IFN-β-1a subcutaneously three times per week. The primary endpoint is the protocol-defined ARR at 2 years (96 weeks).

Study WA25046 is a multicenter, randomized, parallel-group, placebo-controlled study in patients with PPMS. Patients receive 600 mg IV ocrelizumab every 24 weeks as two 300-mg infusions 2 weeks apart or placebo. The primary objective of this study is to evaluate the effectiveness and safety of ocrelizumab compared with placebo. The primary endpoint in this study is the time to onset of confirmed disability progression (CDP) as measured by a pre-specified increase in Expanded Disability Status Scale (EDSS) score (see Appendix 3), sustained for at least 12 weeks.

Study WA21493 was a Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex (IFN-β-1a) controlled, dose-finding study to evaluate the effectiveness, as measured by brain MRI lesions, and safety of two dose regimens of ocrelizumab in patients with RRMS. Results from the completed Phase II study showed that, at Week 24, ocrelizumab significantly reduced the number of Gd-enhancing lesions on T1-weighted brain MRI and ARR compared with both placebo and the active comparator.

See the Ocrelizumab Investigator's Brochure for additional information.

1.2.1.2 Clinical Safety

Safety in Multiple Sclerosis

The safety data included are from three Phase III studies in RMS (Studies WA21092 and WA21093) and PPMS (Study WA25046) and one Phase II study in RRMS (Study WA21493).

Studies WA21092, WA21093, WA25046, and WA21493 have completed the controlled treatment period and are in open-label extension phase.

In the two RMS Phase III studies (pooled data of Studies WA21092 and WA21093) during the 96-week controlled treatment period, ocrelizumab was well tolerated with lower rates of treatment discontinuations for adverse events in patients treated with ocrelizumab 600 mg (3.5%) than in patients receiving IFN β-1a (6.2%). The proportion of patients with adverse events (83.3% in both groups) as well as the total number of adverse events were similar in the ocrelizumab and the IFN β-1a treatment groups over the 96-week treatment period. The proportion of patients reporting infections was higher in the ocrelizumab group compared with the IFN β-1a group (58.4% vs. 52.4%, respectively). In addition, there were more events of infection in the ocrelizumab group (1224 events) compared with the IFN group (948 events) and these were primarily upper respiratory tract infections of Grade 1 or 2 intensity. The proportion of patients with serious adverse events was lower in the ocrelizumab treatment group than in the IFN β-1a treatment group (6.9% in the ocrelizumab treatment group vs. 8.7% in the

IFN β-1a treatment group). Overall, the proportion of patients with serious infections was lower in the ocrelizumab group (1.3%) than in the IFN β-1a group (2.9%). Two serious infusion-related reactions (IRRs) were reported; one in the IFN β-1a group (Grade 3) and one in the ocrelizumab group (Grade 4). As expected, the proportion of patients experiencing IRRs were increased in the ocrelizumab group (34.3%) compared with the active control group (9.7%) who received dummy infusions. During the 96-week controlled treatment period, a total of 6 malignancies were reported, 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFN β-1a treatment group and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer, and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group. During the 96-week controlled treatment period, three deaths occurred in Studies WA21092 and WA21093; 2 patients (suicide and mechanical ileus) in the IFN β-1 treatment group and 1 patient (suicide) in the ocrelizumab treatment group.

In the PPMS Phase III, double-blind, placebo-controlled Study WA25046, ocrelizumab was well tolerated with a similar proportion of patients with adverse events leading to discontinuation from treatment (4.1%) compared with the placebo group (3.3%). The proportion of patients who experienced at least one adverse event was 90% in the placebo group compared with 95% in the ocrelizumab group. Taking into account that twice as many patients were randomized to ocrelizumab than placebo, the number of adverse events experienced by patients with an adverse event was similar (1762 events in the placebo group and 3690 events in the ocrelizumab group). The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The proportion of patients with serious infections was similar in both groups: 5.9% in the placebo group compared with 6.2% in the ocrelizumab group. As expected, the proportion of patients who reported an IRR was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group. During the 96-week controlled treatment period, a total of 15 malignancies in 13 patients were reported: 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients (0.8%) in the placebo group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large-cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group. The proportion of patients with serious adverse events (22.2% in the placebo group compared with 20.4% in the ocrelizumab group) was similar in both groups. There were 5 deaths during the controlled treatment period, one in the placebo group (road traffic accident) and 4 in the ocrelizumab group (pulmonary embolism, pneumonia, pancreatic carcinoma, pneumonia aspiration).

In the RRMS Phase II study WA21493, treatment with 300 mg × 2 and 1000 mg × 2 ocrelizumab was generally well tolerated. The single most common adverse event by Preferred Term was IRR, reported by more ocrelizumab-treated patients compared with

placebo. The proportion of patients reporting IRRs was higher in ocrelizumab-treated patients after the first infusion on Day 1 of the study (9.3% in placebo arm, 34.5% in the 300-mg $\times$ 2 arm, and 43.6% in the 1000-mg $\times$ 2 arm). Rates of infections and serious infections were similar in the ocrelizumab arms compared with placebo. The rate of infections remained consistent throughout the study, including the treatment period (up to Week 96) and the treatment-free period (up to Week 144). There was one malignancy (breast cancer) reported in Study WA21493 in the ocrelizumab group. The adverse event profile of ocrelizumab during the open-label treatment period up to Week 96 and during follow-up and monitoring/observation periods up to Week 144 was consistent with observations during the first 24 weeks.

A total of 3 deaths were reported in RRMS Study WA21493 up to the time of the Investigator's Brochure update in November 2015. Two fatalities occurred after completion of the study treatment and during the Safety Follow-up Period when B cells had already repleted.

See the Ocrelizumab Investigator's Brochure for additional information regarding safety.

1.2.1.3 Clinical Activity

Study WA25046 met its primary endpoint of CDP sustained for at least 12 weeks, showing that treatment with ocrelizumab significantly reduced the progression of clinical disability for 12 weeks compared with placebo (risk reduction: 24%; hazard ratio: 0.76; 95% confidence interval [CI]: $0.59 - 0.98$; $p = 0.0321$). The study also met its key secondary endpoints. Time to CDP sustained for 24 weeks was significantly ($p = 0.0365$) reduced with ocrelizumab compared with placebo (risk reduction: 25%). Change in the 25-foot timed walk from baseline to Week 120 had a significantly ($p = 0.0404$) reduction of 29% with ocrelizumab. Percent change in total volume of T2 lesions on MRI from baseline to Week 120 was significantly ($p < 0.0001$) improved with ocrelizumab (decrease of 3.4%) compared with placebo (increase of 7.4%). Finally, percent change in whole brain volume from Week 24 to Week 120 was significantly ($p < 0.0206$) improved with ocrelizumab (17.5% reduction) compared with placebo.

Study WA21493 results at Week 24 demonstrated that both doses of ocrelizumab achieved the primary endpoint by significantly reducing the number of Gd-enhancing lesions compared with placebo ($p < 0.0001$). Both ocrelizumab dose groups showed statistically significant reductions in ARR compared with the placebo group (ARR = 0.125 for the ocrelizumab 300 mg $\times$ 2 group [$p = 0.0005$] and ARR = 0.169 for the ocrelizumab 1000 mg $\times$ 2 group [$p = 0.0014$]) compared with ARR = 0.637 for the placebo group, representing a relative reduction (RR) of 80% and 73% in ARR versus placebo group for the low- and high-dose ocrelizumab groups, respectively. In exploratory analyses, both ocrelizumab groups were superior to the IFN-β-1a group for the primary endpoint ($p < 0.0001$) and the 300 mg $\times$ 2 group for ARR (ARR = 0.364 for the IFN-β-1a group, representing an RR of 66% in ARR [$p = 0.03$] for the ocrelizumab 300 mg $\times$ 2 group

versus the IFN-β-1a group and an RR of 53.6% in ARR [p = 0.086] for the ocrelizumab 1000 mg × 2 group versus the IFN-β-1a group) (Kappos et al. 2011).

Patients from both the placebo and IFN-β-1a groups switched to ocrelizumab 300 mg × 2 after Week 24. By 48 weeks, the level of benefit of ocrelizumab in reduction of ARR was maintained, where the patients in the ocrelizumab 300 mg × 2 group continued to have a suppressed ARR of 0.086 from Week 24 to 48, and patients who switched to ocrelizumab from either placebo or IFN-β-1a derived a similar degree of efficacy to those randomized to ocrelizumab from onset (ARR for placebo to ocrelizumab = 0.161 and for IFN-β-1a to ocrelizumab = 0.137 after the switch, representing an RR of 74% and 62.4% compared with ARR before the switch, respectively). From baseline to Week 72, patients originally randomized to ocrelizumab 300 mg × 2 maintained clinical efficacy, with an ARR of 0.186.

In studies WA21092 and WA21093, ocrelizumab was superior to IFN-β-1a in reducing the three major markers of disease activity over the two-year controlled treatment period. The studies met their primary endpoint of significantly reducing ARR, with a 50% reduction in the ocrelizumab group compared with the IFN-β-1a group over the two-year period. Additionally, the studies met their secondary endpoints of significantly delaying CDP (loss of physical abilities, measured by the EDSS) by approximately 40% sustained for both 12 and 24 weeks with ocrelizumab compared with IFN-β-1a in pre-specified, pooled analyses of the two studies (p = 0.0006 and p = 0.0025, respectively). Patients in the ocrelizumab group also had significantly reduced acute multiple sclerosis MS-related inflammation and brain injury (total number of T1 Gd-enhancing lesions measured by MRI) at 24, 48, and 96 weeks by more than 90% and the emergence of more chronic or growing areas of MS-related brain injury (T2 hyperintense lesions) at 24, 48, and 96 weeks by approximately 80% compared with patients in the IFN-β-1a group.

See the Ocrelizumab Investigator's Brochure for additional information regarding efficacy.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study will evaluate the effectiveness and safety of using ocrelizumab in patients with RRMS who show a suboptimal response to an adequate course of a DMT.

1.4 *SUBSTUDY RATIONALE*

The optional shorter infusion substudy will evaluate the safety and tolerability of ocrelizumab infused over a shorter time period than the approved administration rate.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the effectiveness of ocrelizumab 600 mg IV every 24 weeks over 96 weeks in patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

A suboptimal response is defined by having one or more clinically reported relapse(s), OR one or more T1 Gd-enhanced lesion(s), OR two or more new or enlarging T2 lesions on MRI despite being on a stable dose of the same DMT for at least 6 months. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT.

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks in patients with RRMS who have had a suboptimal response to an adequate course of a DMT as measured by the nature and incidence of adverse events.

2.3 EXPLORATORY OBJECTIVE

The exploratory objective of this study is to further assess the effectiveness of ocrelizumab by monitoring patient-reported outcomes (PROs) related to quality of life and treatment satisfaction.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This study is a prospective, multicenter, open-label, effectiveness and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. This study will be conducted in North America. An adequate course of prior DMT is defined as the same DMT administered for at least 6 months. Ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion every 24 weeks for the study duration.

Patients will be assessed for effectiveness and safety every 24 weeks as described in the schedule of activities presented in Appendix 1.

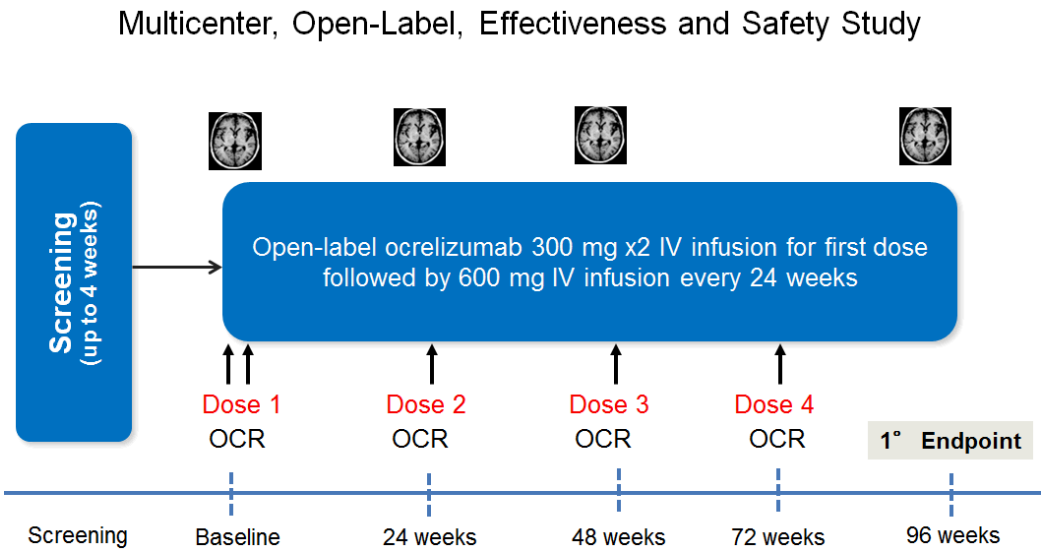
The study will consist of the following periods, described in detail below:

- Screening Period: Up to 4 weeks
- Treatment Period: Open-label treatment period of *72* weeks (4 doses)

- Safety Follow-up Period: Observation *24 weeks* after the last infusion of study drug for patients who discontinue or who choose not to continue with commercially available ocrelizumab at the end of study

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

Figure 1 Overview of Study Procedures



IV = intravenous; OCR = ocrelizumab.

Note: The screening period will last up to 4 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. Baseline MRI results must be available prior to the first infusion.

3.2 SCREENING

Patients screened for this study should not be withdrawn from their current therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy for non-medical reasons should be informed of other approved treatment options before deciding to enroll in the study.

After providing written informed consent, patients will enter a screening period to be evaluated for eligibility. The screening period will last up to 4 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. Re-screening of a patient is allowed once. See Appendix 1 for the assessments to be performed at screening.

3.3 TREATMENT PERIOD

Eligible patients will be treated with an initial 600-mg dose as two 300-mg infusions separated by 14 days (i.e., Days 1 and 15) with subsequent doses administered as one

600-mg infusion every 24 weeks for the study duration. A total of 4 doses will be administered to study participants during the treatment period.

3.4 *OPTIONAL SHORTER INFUSION SUBSTUDY*

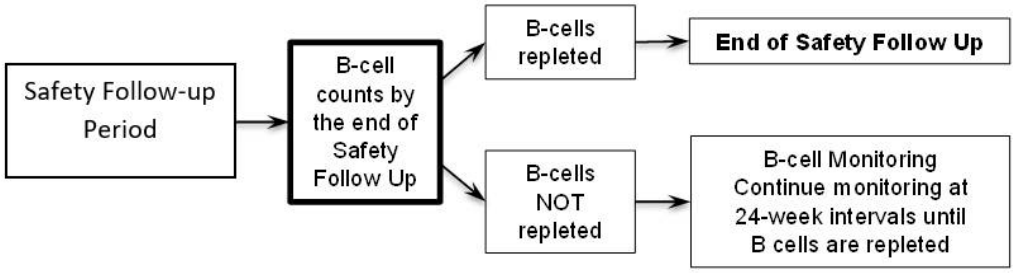
Eligible patients may choose to participate in an optional shorter infusion substudy at the Week 96 visit, during which they will receive ocrelizumab infused over a shorter time period than the approved administration rate. See Appendix 2 *for substudy details.*

3.5 SAFETY FOLLOW-UP PERIOD

Patients who *complete their infusion at Week 72 or who* discontinue from treatment early should enter the Safety Follow-up Period and be assessed *at 24* weeks. *I*f the peripheral blood B-cell count remains depleted *after 6 months from the date of the last infusion*, *the investigator may want to continue* monitoring *the* B-cell count *until it* has returned to the baseline value or to the lower limit of the normal range, whichever is lower. During the Safety Follow-up Period, patients who receive other B-cell targeted therapies will only be followed for an additional period of approximately *24* weeks from the start of the alternative MS treatment.

Figure 2 provides an overview of the Safety Follow-up Period, which is the variable B-cell monitoring period.

Figure 2 Safety Follow-up: Variable B-Cell Monitoring Period



Note: Patients who complete the*ir infusion at Week 72 or who discontinue from treatment early* should enter the Safety Follow-up Period and be assessed *at* 24 weeks. *If the peripheral blood B-cell count remains depleted after 6 months from the date of the last infusion, the investigator may want to continue monitoring the B-cell count until it has returned to the baseline value or to the lower limit of the normal range, whichever is lower.* During the Safety Follow-up Period, patients who receive other B-cell targeted therapies will only be followed for an additional period of approximately *24* weeks from the start of the alternative MS treatment.

During the Safety Follow-up Period, patients will be formally assessed at *a* clinical visit 24 weeks *after their last infusion*. Any data (i.e., from scheduled or unscheduled visits) collected after the patient withdrew from study treatment until the patient completes the

24-week Safety Follow-up Period, or until the patient decides to discontinue from the study entirely, is considered to be safety follow-up. If *the peripheral blood B-cell count remains depleted after 6 months from the date of the last infusion, the investigator may want to continue monitoring the B-cell count until it has returned to the baseline value or to the lower limit of the normal range, whichever is lower.* See Appendix 1 for further details.

Every effort should be made to have patients withdrawing from the treatment complete the *24*-week Safety Follow-up Period and all related assessments.

3.6 END OF STUDY AND LENGTH OF STUDY

The end of the treatment period is defined as the date when the last patient, last visit (LPLV) at 96 weeks occurs. *For patients who enter the substudy, the end of the treatment period occurs approximately at Week 100.*

The total length of the *study* is expected to be approximately 4 years from the first patient enrolled to LPLV.

The end of study is defined as the LPLV of the safety follow-up.

3.7 PLANNED TOTAL SAMPLE SIZE

This study will enroll approximately 600 patients. Please refer to Section 6.1 for more details.

3.8 RATIONALE FOR STUDY DESIGN

3.8.1 Rationale for Ocrelizumab Dose and Schedule

The first dose of ocrelizumab will be administered as two 300-mg IV infusions separated by 14 days, to reduce IRRs. The remaining doses will be administered as single 600-mg doses every 24 weeks.

This dosing regimen is anticipated to be well tolerated and is consistent with the dosing regimen used in Studies WA21092 and WA21093 in patients with RMS (see Section 1.2.1).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 600 patients with RRMS who fulfill the eligibility criteria listed below may participate in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a definite diagnosis of MS, confirmed per the revised 2010 McDonald criteria (Polman et al. 2011; Appendix 4), and have the relapsing remitting form of MS
- Have a length of disease duration, from first symptom, of ≤ 12 years
- Have been treated with an adequate course of treatment with no more than three prior DMTs
  - Adequate treatment is defined as ≥ 6 months on a DMT.
  - Discontinuation of the most recent adequately used DMT must have been due to suboptimal response as defined below.
- Suboptimal response while on his/her last adequately used DMT (for ≥ 6 months); a suboptimal response is defined by having one of the following qualifying events despite being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new or enlarging T2 lesions on MRI

  These qualifying events must have occurred while on the last adequately used DMT. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event must have occurred within the last 12 months of treatment with this DMT from the date of screening.
- EDSS of 0 to 5.5, inclusive, at screening
- For women of childbearing potential: agreement to *use an acceptable birth control method:*
  - *Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action*
  - *Male or female condom with or without spermicide*
  - *Cap, diaphragm, or sponge with spermicide*
  - *A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods are also considered acceptable, but not highly effective, birth control methods)*

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of PPMS, PRMS, or SPMS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to claustrophobia, weight, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gd-enhancing ligands, etc.).

- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - History of progressive multifocal leukoencephalopathy (PML)
- Pregnancy or lactation, or intention to become pregnant during the study
  - Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to initiation of study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, and gastrointestinal or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] Class III/IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease but excluding fungal infection of nail beds) or any severe 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
- History of or currently active primary or secondary immunodeficiency

- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, tuberculosis)
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of malignancy, including solid tumors and hematological malignancies, except basal cell, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been excised with clear margins
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- History of coagulation disorders
- History of alcohol or drug abuse within 24 weeks prior to screening
- Previous treatment with natalizumab within 12 months prior to screening unless failure was due to confirmed, persistent ADAs
  - Patients previously treated with natalizumab will be eligible for this study only if duration of treatment with natalizumab was $<$ 1 year and natalizumab was not used in the 12 months prior to screening. Anti-JCV antibody status (positive or negative) and titer (both assessed within the year of screening) must be documented prior to enrollment. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay (e.g., ELISA).
- Previous treatment with systemic cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate
- Treatment with IV immunoglobulin within 12 weeks prior to baseline
- Treatment with dalfampridine (Ampyra®) unless on stable dose for $\geq$ 30 days prior to screening
  - Wherever possible, patients should remain on stable doses throughout the treatment period.
- Receipt of a live vaccine within 6 weeks prior to baseline; in rare cases when patient requires vaccination with a live vaccine, the screening period may need to be extended but cannot exceed 8 weeks
- Systemic corticosteroid therapy within 4 weeks prior to screening
  - The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for their MS before screening.
  - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- Previous treatment with fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) in patients whose lymphocyte count is below the lower limit of normal (LLN)
- Contraindications to or intolerance of oral or IV corticosteroids, including IV methylprednisolone (or equivalent steroid) administered according to the country label, including:
  - Psychosis not yet controlled by a treatment

- Hypersensitivity to any of the constituents preceding

- Treatment with alemtuzumab (Lemtrada®)
- Treatment with a B-cell targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental (Exception: treatment with an experimental drug that was subsequently approved in the patient's country is allowed.)
- Laboratory test results as follows:
  - Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C antibody (HepCAb)
  - Lymphocyte count below LLN
  - CD4 count $< 300/\mu L$
  - AST or ALT $\geq 3.0 \times$ the upper limit of normal (ULN)
  - Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
  - Total neutrophil count below LLN

    Re-testing before baseline: in rare cases in which the screening laboratory samples are rejected by the laboratory (e.g., hemolyzed sample) or the results are not assessable (e.g., indeterminate) or abnormal, the tests need to be repeated. Any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before enrollment must meet study criteria. In such circumstances, the screening period may need to be prolonged but should not exceed 8 weeks.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study in which all patients will receive the 600-mg dose of ocrelizumab following the 24-week regimen. Therefore, no randomization or blinding will be used in this study.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 4% trehalose dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I USP, glass vial fitted with a 20-mm, fluoro-resin, laminated

stopper and an aluminum seal with a flip-off plastic cap and contains a nominal 300 mg ocrelizumab. No preservative is used as each vial is designed for single use.

The ocrelizumab drug product must be diluted before administration. Solutions of ocrelizumab for IV administration are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride to a final drug concentration of 1 to 2 mg/mL.

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. 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 up to 0.2 micrometer).

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2–8°C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2–8°C. Infusion solution must be completely administered to the patient within 32 hours of preparation (not exceeding 24 hours at 2–8°C and 8 hours at room temperature). In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks for a maximum of 4 doses.

Although ocrelizumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Ocrelizumab infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits.

Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300-mg dose and approximately 210 minutes (3.5 hours) for the 600-mg dose. To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent steroid), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an

antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each ocrelizumab infusion.

Refer to Section 5.1.1 and Section 5.1.2 for the risks associated with these mandatory premedications.

It is also strongly recommended that the infusion is accompanied by prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30 – 60 minutes prior to the start of an infusion to reduce potential IRRs.

Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.

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.

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.

See the Ocrelizumab Investigator's Brochure for detailed instructions on drug preparation, storage, and administration.

An overview of the ocrelizumab dosing is presented in Table 1.

Table 1 Overview of Ocrelizumab Dosing

	1st Dose [a,c]		2nd Dose [b,c]	3rd Dose [c]	4th Dose
	(Weeks 1 – 24)		(Weeks 24 – 48)	(Weeks 48 – 72)	(Weeks 72 – 96)
Group	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion
Ocrelizumab	300 mg IV	300 mg IV	600 mg IV	600 mg IV	600 mg IV

IV = intravenous.
Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistamine will be administered to reduce the potential for IRRs. Each treatment period has a duration of 24 weeks. The treatment period consists of *up to* 96 weeks of treatment; patients will receive a maximum of 4 treatment cycles.
[a] The first dosing will consist of two IV infusions separated by 14 days (i.e., Days 1 and 15).
[b] Beginning with the second dose, a single infusion of ocrelizumab will be administered.
[c] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Because of possible need to vary infusion rates depending on tolerance of the infusion, the total infusion time may exceed the time stated. **Unless an IRR occurs necessitating discontinuation, the entire contents of the infusion bag must be administered to the patient.**

Guidelines for treatment discontinuation are provided in Section 4.6.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Mandatory Premedication: Methylprednisolone and Antihistaminic Drug

Premedicate with 100-mg methylprednisolone (or equivalent) completed approximately 30 minutes prior to each ocrelizumab infusion and with an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of IRRs.

Any overdose or incorrect administration of methylprednisolone should be noted on the Pre-infusion Treatment eCRF. Adverse events associated with an overdose or incorrect administration of methylprednisolone or antihistamine should be recorded on the Adverse Event eCRF, with signs and symptoms also recorded on the dedicated Infusion-Related Reaction eCRF.

4.3.4 Other Prophylactic Treatment

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered to further reduce the frequency and severity of IRRs.

4.3.5 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (ocrelizumab) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the interactive voice/Web response system (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 returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any unused 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.

4.3.6 Post-Trial Access to Ocrelizumab

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide ocrelizumab or any other study treatments or interventions to patients who have completed the study, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period (see Appendix 1).

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

- Anti-hypertensive medications
  - Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.
- Corticosteroids
  - Patients who experience a relapse may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. Such patients should not discontinue study treatment solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal (Section 4.6.2).

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the program and for at least 7 days prior to initiation of ocrelizumab, unless otherwise specified below:

- Therapies for MS (see Section 4.1.2 for restrictions prior to initiation of ocrelizumab) other than systemic corticosteroids
- Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers while patient is B-cell depleted

See the Ocrelizumab Investigator's Brochure for a more detailed safety profile.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. 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 by the investigator to confirm that patients meet all eligibility criteria. 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.

4.5.2 Medical History and Demographic Data

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

4.5.3 Physical Examinations

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.

Height and weight will be measured at screening only. See Appendix 1 (schedule of activities) for the timing of these assessments.

4.5.4 Neurological Examinations

Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the study. See Appendix 1 (schedule of activities) for the timing of these assessments.

A protocol-defined relapse is an occurrence of new or worsening neurological symptoms attributable to 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 immediately preceded by a stable or improving neurological state for least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate Functional Systems Score (FSS),

or 1 point on two or more of the appropriate FSS. The change must affect the selected FSS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory, or visual). Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse (Please note: Sexual dysfunction and fatigue need not be scored).

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 6). 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.

4.5.5 Vital Signs

Vital signs will include measurements of heart rate, temperature, and systolic and diastolic blood pressure.

Vital signs should be taken approximately 45 minutes prior to premedication. In addition, vital signs should be obtained prior to the ocrelizumab infusion and then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.5.6 Assessment of Disability

Disability in MS will be measured by the EDSS. See Appendix 1 (schedule of activities) for the timing of these assessments. It is strongly recommended that the same EDSS rater is used for each patient throughout the study when possible. The EDSS should be done on the same day or within 24 hours prior to the study drug infusion if both are done at the same visit.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus “other”) rated and scored as FSSs. 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 (death) (see Appendix 3).

Disability progression is defined as a ≥ 1-point increase in EDSS score from baseline if the baseline EDSS score is between 0.0 and 5.5 (inclusive) or a 0.5-increase from baseline if the baseline EDSS score is higher than 5.5. The increase of disability progression on EDSS should be confirmed 24 weeks after the time at which the increase has been observed. The initial increase in EDSS can occur at any visit during the 96-week *study*.

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions related to MS pathology and potentially other pathology findings. Brain MRI scans 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 PML, 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 patients Screening MRI scan must have been received from the centralized reading center confirming scan passed QC. The brain MRI requires approximately 2 business days 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.

Assessments will include T1-weighted scans before and after injection of Gd contrast, and may also include, but may not be limited to: fluid-attenuated inversion-recovery (FLAIR), proton density-weighted, and T2-weighted scans.

4.5.8 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.

Routine safety laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, RBCs, WBC absolute or differential, ANC, and quantitative platelet count)
- Serum chemistry (AST, ALT, GGT, total bilirubin, urea or BUN, uric acid, creatinine, potassium, sodium, calcium, and phosphorus)
- Urinalysis or urine dipstick on site (standard to assess kidney function)
- Pregnancy test
  - All women of childbearing potential will have a serum or urine 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.

- Viral serology and detection:
  - Hepatitis B (HBsAg and HBcAb confirmed, if positive, by positive viral DNA PCR)
  - For enrolled patients with negative HBsAg and positive total HBcAb, hepatitis B virus (HBV) DNA (by PCR) must be repeated every 24 weeks
  - Hepatitis C virus (HCV) antibody (performed only at screening)

Additional samples will include the following:

- Lymphocyte subtypes
  - Whole-blood samples will be collected to determine the duration of B-cell depletion and recovery (CD19+) and T-cell counts (CD4+, CD8+).

Per local Institutional Review Board (IRB)/Ethics Committees (ECs) requirements, additional testing may be required for selected patients or selected centers to exclude TB, Lyme disease, HTLV-1 associated myelopathy (HAM), AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

4.5.9 Patient-Reported Outcomes

PRO data will be elicited from patients in this study to better characterize patient quality of life and treatment satisfaction while on ocrelizumab. PROs completed at baseline should be in reference to the last-used DMT prior to enrollment.

The Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item questionnaire designed to measure the physical and psychological impact of MS from the patient's perspective. Additionally, the Treatment Satisfaction Questionnaire for Medication (TSQM II) and the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q), questionnaires to assess patients' treatment satisfaction, will be administered to patients during the visits listed in the schedule of activities (see Appendix 1).

Please note that all PROs are 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.

4.5.10 Safety Follow-up Period

Patients who complete their infusion at Week 72 or who discontinue from treatment early should enter the Safety Follow-up Period and be assessed at 24 weeks. If the peripheral blood B-cell count remains depleted after 6 months from the date of the last

infusion, the investigator may want to continue monitoring the B-cell count *until it* has returned to the baseline value or to the lower limit of the normal range, whichever is lower. During the Safety Follow-Up Period, patients who receive other B-cell targeted therapies will only be followed for an additional period of approximately *24* weeks from the start of the alternative MS treatment.

See Figure 2 for an overview of the Safety Follow-up Period and Appendix 1 for the schedule of activities.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to follow dosing instructions or to complete program visits

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Criteria for Re-Treatment with Ocrelizumab

Prior to re-treatment with ocrelizumab, patients will be evaluated for the following conditions and laboratory abnormalities. If any of these are present prior to re-dosing, further administration of ocrelizumab should be suspended until these are resolved or held indefinitely:

- Life-threatening (Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection
- Ongoing pregnancy *or breastfeeding*

4.6.3 Study Treatment Discontinuation

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

- Life-threating IRR or serious hypersensitivity reaction

- Active hepatitis B infection
- PML
- Active TB, either new onset or reactivation

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

4.6.4 Study and Site 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.

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 on Harmonisation (ICH) guidelines for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab is currently in clinical development for the treatment of MS. Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the clinical program. Patient safety during the ocrelizumab program is ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and standard laboratory measurements. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Administration of ocrelizumab will be performed in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. All adverse events and serious adverse events will be recorded during the study for at least 24 weeks after the end of the treatment period and throughout safety follow up. Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v4.0. Safety assessments will be conducted per the schedule of activities in Appendix 1.

The identified and potential safety issues anticipated in this study are reported in the Ocrelizumab Investigator's Brochure. In addition, measures intended to avoid or minimize these issues, are outlined in the following sections.

5.1.1 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.

5.1.2 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.

5.1.3 Risks Associated with Ocrelizumab

5.1.3.1 Identified Risks and Adverse Drug Reactions

5.1.3.1.1 Infusion-Related Reactions

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

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

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

5.1.3.1.2 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% to 6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of RMS patients with serious infections was lower in the ocrelizumab group (1.3%) than in the interferon beta-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 (RA) 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 MS patient treated with ocrelizumab during the controlled period of the pivotal trials.

There were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active hepatitis B virus should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before the 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 5.1.3.2).

5.1.3.1.3 Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Igs) over the controlled period of the studies, mainly driven by reduction in IgM, with no observed association with serious infections. The proportion of patients with decrease in Igs below the 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 (see Potential Risks, Section 5.1.3.2).

5.1.3.1.4 Delayed Return of Peripheral B Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post-treatment (first timepoint of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time 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 their B cells have repleted.

5.1.3.1.5 *Impaired Immunization Response*

The safety of immunization with live or live-attenuated vaccines following ocrelizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

After treatment with ocrelizumab over 2 years, the proportion of patients with positive antibody titers against S. pneumoniae, mumps, rubella, varicella were generally similar to the proportions at baseline.

In a randomized, open-label study, RMS patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. It is still recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunization status of patients before starting treatment with ocrelizumab. Patients who require vaccination should complete their immunizations at least 6 weeks prior to initiation of ocrelizumab. Please see the Ocrelizumab Investigator's Brochure for more details.

5.1.3.2 Potential Risks

5.1.3.2.1 Progressive Multifocal Leukoencephalopathy

PML is an important potential risk for ocrelizumab and it has only been reported with ocrelizumab where the risk for PML was preexisting, specifically because of prior natalizumab treatment. Refer to Appendix 6 for guidance for diagnosis of PML. See the Ocrelizumab Investigator's Brochure for more details.

5.1.3.2.2 Serious Infections Related to Decrease in Immunoglobulins (particularly in patients previously exposed to immunosuppressive/immunomodulatory drugs or with pre-existing hypogammaglobulinemia)

Based on additional patient exposure an apparent association between sustained decrease in immunoglobulins (IgA, IgG, IgM) and serious infections with ocrelizumab treatment was observed. However, no pattern (e.g., type of infections, safety laboratory abnormalities beyond the decrease in Ig, latency, duration) was found that could identify a subset of patients at higher risk of serious infections.

5.1.3.2.3 Hypersensitivity Reactions

No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials.

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.

5.1.3.2.4 Malignancies including Breast Cancer

An increased risk of malignancy with ocrelizumab may exist. In controlled trials in adults with multiple sclerosis, malignancies, including breast cancer, occurred more frequently in ocrelizumab-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 as per local guidelines. See the Ocrelizumab Investigator's Brochure for more details.

5.1.3.2.5 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, and approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified.

Detailed information for all risks can be found in the current Ocrelizumab Investigator's Brochure.

5.1.4 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	• If the event that a patient experiences is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event. • This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.
Severe IRR (or complex of flushing, fever, and throat pain)	• If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. • The infusion should be restarted only after all symptoms have resolved. • The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.

Event	Action to Be Taken
Life-threatening or disabling IRR (e.g., anaphylaxis)	• Immediately stop ocrelizumab if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. • The patient should receive appropriate treatment. • Permanently discontinue ocrelizumab in these patients.

IRR = infusion-related reaction.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guidelines for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest are identified for ocrelizumab in the indicated patient population in Section 5.1.3.1. Standard adverse events of special interest 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 (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 – Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed (see Section 5.4.2).

Unrelated serious adverse events must be collected and reported during the study through the end of the Safety Follow-Up Period, which is at least 24 weeks after the last infusion but may be extended in patients whose B cells take longer to replete. Non-serious adverse events have to be reported until the end of the Safety Follow-up Period.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. 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?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 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 (v4.0), 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 5.4.2 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 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

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

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

Further details on prevention and management of IRRs are described in Section 5.1.3.1.1, Section 5.1.4 (Table 2), and in the Ocrelizumab Investigator’s Brochure.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- 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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified, adverse event, reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of RRMS.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of RRMS, "RRMS progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Relapsing Remitting Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following are not considered serious adverse events:

- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones and diagnostic testing. Such events should still be recorded as medical procedures in the concomitant procedures/treatments eCRF.
- Hospitalization to receive trial medication, such as infusions of ocrelizumab, unless this is prolonged (more than 24 hours)
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.: [redacted] (U.S.)

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported for at least *24* weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within *24* weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Given that there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the end of pregnancy and breastfeeding. Pregnant and breastfeeding patients should continue to follow the schedule of assessments; however, no infusions will occur. If there is a concern with the ability of a pregnant or breastfeeding patient to perform all scheduled assessments, or if an assessment is contraindicated during pregnancy, the investigator must contact the Medical Monitor for further discussion. Restart of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit–risk discussion between the patient and investigator.

Patients who have already permanently discontinued from the study because of pregnancy (or for any other reason) may not be re-enrolled in the study.

For pregnancies occurring in female patients during treatment with ocrelizumab or within 6 months after the last dose of ocrelizumab, pregnancy outcome and health status of the child will be collected until the child is 1 year of age. Data collection is voluntary only; it does not include any interventions or invasive procedures. A Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire will be submitted to Health Authorities and IRB/IECs for their approval, along with the infant data release consent form. The data will be reported on dedicated pregnancy outcome and infant health information paper questionnaire.

5.4.3.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.4 *Reporting Requirements for Cases of Ocrelizumab Accidental Overdose or Medication Error*

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug*

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with ocrelizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- *Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and*

"Medication error" boxes. Enter a description of the error in the additional case details.

- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Adverse events associated with special situations should be recorded as described below for each situation:

- *Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as at least *24* weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Ocrelizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Refer to the Ocrelizumab Investigator's Brochure for a list of serious adverse drug reactions.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

In this single-arm, non-comparative study, the analyses will mostly be descriptive and exploratory. Inferential statistical methods, if applied, will be employed to highlight the data aspect of interest. Unless otherwise specified, statistical tests will be two sided and the statistical significance level will be 5%. Corresponding 95% CIs will be presented as appropriate. No corrections for multiple testing will be applied to the primary endpoint or secondary endpoints analyses as well as to the interim analyses.

For continuous variables, descriptive statistics (e.g., mean, median, standard deviation [SD], n, 25th and 75th percentiles, minimum, maximum) will be calculated and

summarized. For categorical variables, the number and percentage in each category will be displayed. Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database.

Since the number of previous DMTs used may be related to the treatment outcome, the number of previous DMTs used (i.e., 1 vs. 2) will be used as a stratification factor in the summary and analysis. In general, the report will be presented by the number of previous DMTs used and overall; the statistical analysis will be stratified or adjusted for by the number of previous DMTs used along with the corresponding baseline covariate when appropriate. Other subgroups of interest may also be considered in the statistical data analysis.

After the Week 72 visit of the last patient enrolled, approximately 24 weeks may be needed to allow the confirmation of the last protocol-defined event of the 24-week CDP. Therefore, the clinical cut-off date will occur approximately 24 weeks after the last patient's Week 72 visit when the status is clarified for each patient. The sites and EDSS raters will remain available until approximately 24 weeks after the Week 72 visit of the last patient enrolled.

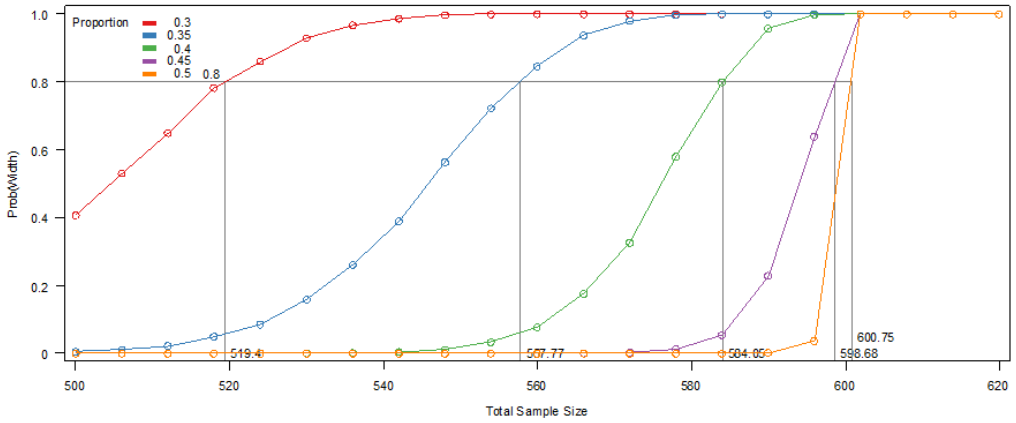
6.1 DETERMINATION OF SAMPLE SIZE

Assuming a) the expected proportion of patients who will be event free during 96 weeks is 45%; b) the type one error rate is 5% and the half-width of 95% CI for the proportion is 4%; c) the probability that half-width of 95% CI is at most 4% is 80%, then the required sample size will be $n = 600$.

It should be noted that the estimation of the proportion of patients who will be protocol-defined event free (45%) is based on the pooled data from Studies WA21092 and WA21093 (OPERA I and OPERA II, respectively) from all patients who had a baseline EDSS of ≥ 2.0. The true proportion could be lower than 45% for ocrelizumab-treated patients who would meet the definition of sub-optimal responders as specified in this protocol. However, the required sample size should be lower than 600 patients to achieve the same precision (i.e., maximum half-width of 95% CI) if the true proportion is actually lower than 45%. This is due to the fact that a lower proportion will have a smaller variance for the estimated proportion than that from 45% and the variance of proportion is maximized when the proportion is 50% (calculation performed using SAS software, Version 9.2). In Figure 3, the sample sizes are displayed from a range of proportions (30% to 50%) with an 80% probability that half-width of 95% CI is at most 4%. For example, if the proportion is 45%, the corresponding sample size is 598.86 (rounded to 600 for recommended number). The ranges of proportion were based on the 2-year proportion of alemtuzumab-treated patients and natalizumab-treated patients who achieved no evidence of disease activity (NEDA) (32% and 55%, respectively). In Figure 4, the sample sizes are displayed similarly to Figure 3, but the

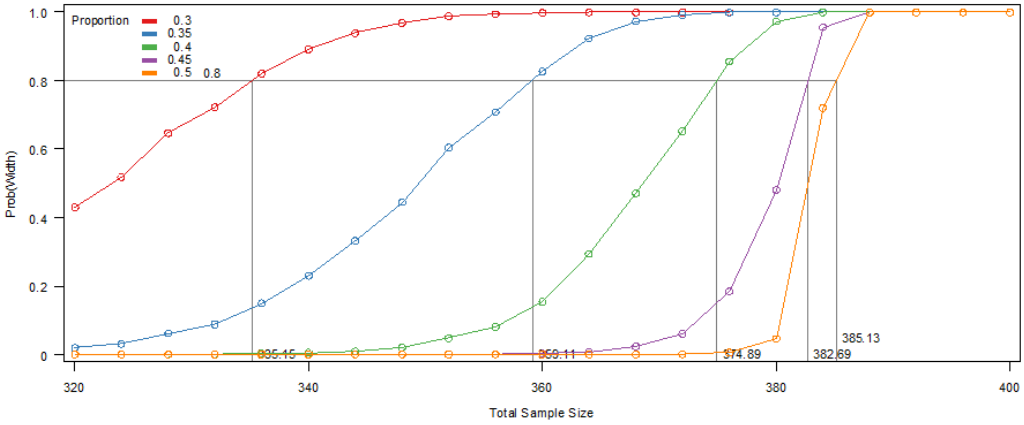
half-width of 95% CI is set as 5% for providing additional information concerning the impact of half-width on sample size.

Figure 3 Prob(Half-width of 95% CI≤4%) with Sample Size if Expected Proportion=30%–50%



Source: Hartung et al. 2013; Prosperini et al. 2012; Internal OPERA study data.
CI = confidence interval.

Figure 4 Prob(Half-width of 95% CI≤5%) with Sample Size if Expected Proportion=30%–50%



Source: Hartung et al. 2013; Prosperini et al. 2012; Internal OPERA study data.
CI = confidence interval.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, ocrelizumab administration, and discontinuations from the study will be summarized. Patient disposition and the incidence of treatment discontinuation for

reasons other than disease progression will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics, medical history, and neurological examination will be summarized. MS disease history (duration since MS first symptom, duration since MS diagnosis), MS disease status (MS treatment naïve or experienced), and MS prior treatment (for those being treated) will be summarized. Also, the baseline measures of MRI, EDSS, or other important endpoints will be summarized.

6.4 ANALYSIS POPULATIONS

The efficacy analyses will be performed using the intent-to-treat (ITT) population. The per-protocol (PP) population will be used for supportive efficacy analyses (for the primary endpoint and selected secondary endpoints) in order to evaluate the influence of major protocol violators on key efficacy endpoints. The safety population will be used for safety analyses.

6.4.1 Intent-to-Treat Population

All enrolled patients who receive any ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason and who did not perform any assessment for any reason will still be included in the ITT population.

6.4.2 Per-Protocol Population

The PP population will include all patients in the ITT population who adhere to the protocol. Specific reasons for warranting exclusion will be agreed to by the study team and documented in the SAP.

6.4.3 Safety Population

The Safety Population will include all enrolled patients who received any ocrelizumab.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Outcome Measures

The primary efficacy assessment will be the proportion of patients who are free of any protocol-defined events during a 96-week $study$. The definition of a protocol-defined event is the occurrence of at least one of the following while on treatment with ocrelizumab:

- A protocol-defined relapse as defined in Section 4.5.4 (Note: An adjudication of protocol-defined relapses will be performed by the Sponsor based on pre-specified criteria, applied to data collected by the investigator.)
- A T1 Gd-enhanced lesion on brain MRI
- A new and/or enlarging T2 lesion on brain MRI

- CDP (24 weeks)

6.5.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- The proportion of patients free from a protocol-defined event during a 24-week period and a 48-week period
- Time to protocol-defined event (see definition above)
- Annualized relapse rate at Week 96
- The time to onset of first relapse
- Time to onset of first T1 Gd-enhanced lesion
- Time to onset of first new and/or enlarging T2 lesion
- Time to onset of CDP for at least 24 weeks during the study period
- Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48, and 96
- Change in total T2 lesion volume detected by brain MRI from baseline to Weeks 24, 48, and 96
- Total number of new and/or enlarging T2 lesions detected by brain MRI at Weeks 24, 48, and 96

6.5.3 Exploratory Outcomes

The exploratory outcomes will consist of the following:

- PRO
  - MSIS-29
  - SATMED-q
  - TSQM II

6.5.4 Analysis Methods

The proportion of patients who are free from a protocol-defined event during Week 96 (the primary efficacy endpoint) will be calculated, and the two-sided 95% CI will be presented. Data from any unscheduled visit within each respective 24-week interval will be included for this endpoint. Similar analyses will be applied to the proportions of patients who are free from a protocol-defined event during Weeks 24 and 48.

The annualized relapse rates by Week 96 will be analyzed using negative binomial model, adjusting for the number of previous DMTs used and including the log-transformed year of drug exposure time as an “offset” variable. The adjusted annualized relapse rate and the two-sided 95% CI for the relapse rate will be presented.

The Kaplan-Meier estimator (i.e., the product limit estimator) will be used to estimate the survival function for time-to-event data (e.g., time to protocol-defined event; time to onset

of first relapse; time to onset of CDP for at least 24 weeks). The proportion of patients with an event and of those censored will be reported; the median survival time and its 95% CI will be presented.

The total number of T1 Gd-enhanced lesions will be calculated as the sum of the individual number of T1 Gd-enhanced lesions at Weeks 24, 48, and 96. Data from other unscheduled assessments will not be included in this summary or analysis. A negative binomial model will be used to estimate the rate of lesion occurrence. In order to account for patients receiving varying numbers of brain MRI scans during the study, the log-transformed number of brain MRI scans received will be included in the model as an "offset" variable for appropriate computation.

The change from baseline in total T2 lesion volume as detected by brain MRI to Weeks 24, 48, and 96 will be analyzed through a mixed model with repeated measure (MMRM), adjusting the following covariates: baseline score and the number of previous DMT use.

The total number of new and/or enlarging T2 lesions will be calculated as the sum of the individual number of new and/or enlarging T2 lesions at Weeks 24, 48, and 96. Data from unscheduled assessments will not be included in this summary or analysis. The analysis model will be similar to that used for the total number of T1 Gd-enhanced lesions.

The PRO outcomes and other exploratory endpoints will be descriptively summarized as change from baseline at Weeks 24, 48, and 96 if they are continuous variables (e.g., MSIS-29) or summarized in the number and percentage of events by each visit if they are dichotomized or categorical variables. To assess the longitudinal treatment effect for continuous variable, the mean changes from baseline at Weeks 24, 48, and 96 will be analyzed through a MMRM adjusting the following covariates: baseline score and the number of previous DMTs used.

6.6 SAFETY ANALYSES

6.6.1 Safety Outcome Measures

The safety outcome measures comprise the following: the incidence and nature of all adverse events, including findings on vital sign measurements, physical and neurological examinations, clinical laboratory tests, locally reviewed MRI for safety (non-MS CNS pathology), and concomitant medications.

6.6.2 Safety Analyses

Safety will be assessed through summaries of adverse events (including incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities.

All adverse events occurring on or after treatment on Day 1 will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for

individual adverse events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from the study due to an adverse event, adverse events leading to infusion adjustment, and treatment-related adverse events will be summarized. In addition, all serious adverse events and deaths will be listed.

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

Ocrelizumab exposure will be summarized, including duration and dosage.

6.7 HANDLING OF MISSING DATA

The following guideline will be used when dealing with missing data related to the protocol-defined event in the primary efficacy endpoint. Patients who complete the treatment period will be considered as having a protocol-defined event if any of the following are reported during the 96-week *study*: at least one protocol-defined relapse, Gd-enhancing T1 lesions, new and/or enlarging T2 lesions, or CDP. Otherwise, the patient will be considered as being protocol-defined event free.

Patients who discontinue treatment early and have at least one event before early discontinuation will be considered as having a protocol-defined event. *Details of missing data handling for p*atients who discontinue treatment early and do not have any event before early discontinuation will be specified in Statistical Analysis Plan.

6.8 INTERIM ANALYSES

It is estimated that two to three interim analyses will be performed during the course of the study, according to patient enrollment and availability of data of interest. Interim analyses may be used for internal decision making, hypothesis generation, abstraction/publication for major MS conferences, or other purposes, as applicable. Details on the timing and scope of interim analyses will be described in the Statistical Analysis Plan.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Local laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S.

Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study 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.

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 national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and study drug shipments.

Patient data will be recorded via an EDC system using eCRFs.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site: http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

	Screening	Treatment Period					*Safety Follow-up Visit* [b]	Early Withdrawal Visit [c]	Unscheduled Visit (due to relapse) [d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	*7*		
Week	**–4** [a]	**–**	**2**	**24**	**48**	**72**	*96*		
Study Day (window in days)	**–28**	**1 Baseline**	**15 (± 2)**	**169 (± 14)**	**337 (± 14)**	**505 (± 14)**	*673 (± 14)*		
Informed consent [e]	x								
Medical history and demographic data [f]	x								
Review inclusion and exclusion criteria	x	x							
Physical examination [g]	x	x	x	x	x	x	x	x	x
Height	x								
Weight	x								
Vital signs [h]	x	x	x	x	x	x	x	x	x
Laboratory Assessments [i]									
Hematology, chemistry, urinalysis [j]	x	x [k]		x	x	x	x	x	
Pregnancy test [l]	x	x	x	x	x	x	x	x	
Hepatitis screening [m]	x								
Hepatitis B virus DNA test [m]	x			x	x	x	x	x	
Lymphocyte subtypes [n]	x			x	x	x	x	x	
EDSS score	x	x [k]		x [o]	x [o]	x [o]	x	x	x
Neurological examination [p]	x	x	x	x	x	x	x	x	x
Patient-Reported Outcome Assessments [q]		x		x	x	x		x	

Appendix 1
Schedule of Activities (cont.)

Visit Number	Screening 1	Treatment Period 2	3	4	5	6	Safety Follow-up Visit [b] 7	Early Withdrawal Visit [c]	Unscheduled Visit (due to relapse) [d]
Week	–4 [a]	–	2	24	48	72	96		
Study Day (window in days)	–28	1 Baseline	15 (± 2)	169 (± 14)	337 (± 14)	505 (± 14)	673 (± 14)		
Brain MRI [r]		x [s]		x [o]	x [o]		x	x [c]	
Recording of potential relapses		x	x	x	x	x	x	x	x
Adverse event assessment [t]		x	x	x	x	x	x	x	x
Concomitant treatment review		x	x	x	x	x	x [u]	x	x
Methylprednisolone and antihistamine premedication [v]		x	x	x	x	x			
Ocrelizumab administration [w]		x	x	x	x	x			

β-hCG = beta human chorionic gonadotropin; 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 antibody; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; QC = quality control.

[a] The screening period will last up to 4 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons.

[b] The Safety Follow-up Period will begin when the patient completes their infusion at Week 72 or discontinues from treatment early. Patients will be assessed at 24 weeks (at Week 96). If the peripheral blood B-cell count remains depleted after 6 months from the date of the last infusion, the investigator may want to continue monitoring the B-cell count until it has returned to the baseline value or to the lower limit of the normal range, whichever is lower. During the Safety Follow-up Period, patients who receive other B-cell targeted therapies will only be followed for an additional period of approximately 24 weeks from the start of the alternative MS treatment.

[c] When a patient discontinues treatment, all assessments must be completed/obtained, except for MRI if done within the past 8 weeks unless clinically indicated.

Appendix 1
Schedule of Activities (cont.)

[d] Additional assessments may be conducted, as determined by the investigator, in order to investigate adverse events.

[e] Written informed consent will be obtained from all patients during screening in order to be eligible for the study.

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

[g] 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.

[h] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken approximately 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

[i] Needs to be available prior to dosing (to be taken up to 14 days prior to dosing). In rare cases in which the result is not assessable (e.g., indeterminate) or is abnormal, the tests need to be repeated. Any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition.

[j] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute or differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, total bilirubin, urea or BUN, uric acid, creatinine, potassium, sodium, calcium, and phosphorus. Urinalysis or urine dipstick will be used to assess kidney function.

[k] If the screening assessments have been conducted/obtained within 14 days prior to dosing, respective baseline assessments do not need to be repeated prior to dosing.

[l] 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.

[m] All patients must have negative HBsAg result and negative HepCAb screening tests prior to enrollment in the study. If the total HBcAb is positive at screening, HBV DNA measured by PCR must be negative in order for a patient to be eligible for the study. For enrolled patients with negative HBsAg and positive total HBcAb, HBV DNA (by PCR) must be repeated every 24 weeks.

[n] Whole-blood samples will be collected to determine the duration of B-cell depletion and recovery (CD19+) and T-cell counts (CD4+, CD8+).

[o] To be obtained/performed before administration of ocrelizumab (i.e., pre-dose).

Appendix 1
Schedule of Activities (cont.)

[p] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. 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, cerebellar symptoms/sings (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 6). A patient with confirmed PML should be withdrawn from the study.

[q] PRO assessments will consist of the following: Multiple Sclerosis Impact Scale 29 (MSIS-29), the Treatment Satisfaction Questionnaire for Medication (TSQM II), and the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q). PROs completed at baseline should be in reference to the last-used DMT prior to enrollment. Please note that all PROs are 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.

[r] Should only be done at scheduled visits unless PML is suspected.

[s] MRI has to be conducted before the baseline visit, and results must be available prior to treatment. Prior to initiation of treatment on Day 1/Baseline, a QC report for the baseline MRI scan must have been received from the centralized reading center confirming scan passed QC. The brain MRI requires approximately 2 business days to be quality checked before dosing of ocrelizumab.

[t] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Unrelated serious adverse events must be collected and reported during the study through the end of the Safety Follow-up period, which is at least 24 weeks after the last infusion but may be extended in patients whose B cells take longer to replete. Non-serious adverse events have to be reported until the end of the Safety Follow-up Period.

[u] Medications used after treatment discontinuation should be recorded during the Safety Follow-up Period.

[v] All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab. Prophylactic treatment with an analgesic/antipyretic (e.g., 1 g acetaminophen) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.

[w] Dose 1 of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) separated by 14 days (i.e., Days 1 and 15). Subsequent doses will be administered as one 600-mg IV infusion every 24 weeks for a maximum of 4 doses.

Appendix 2
Optional Shorter Infusion Substudy

BACKGROUND AND RATIONALE

Ocrevus® (ocrelizumab) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS). According to the currently approved U.S. label, ocrelizumab must be administered at a 600-mg dose through slow intravenous (IV) infusion. The first dose is given as two doses, separated by 14 days, and administered as two 300-mg infusions over the course of 2.5 hours, while subsequent doses are given as a single 600-mg infusion over 3.5 hours. This substudy will explore the effect of a shorter infusion of ocrelizumab on the rate and severity of IRRs.

The most common safety events reported with ocrelizumab are IRRs. IRRs occur more frequently during the first infusion of the first dose. The majority of IRRs (>90% of patients reporting IRRs) were of mild to moderate intensity, and the intensity of IRRs decreased with subsequent dosing. The most frequently reported IRR symptoms during infusion in the ocrelizumab group were pruritus, rash, throat irritation, and flushing (33.0%, 29.2%, 29.8%, and 16.8% of patients with IRR, respectively) (see the Ocrelizumab Investigator's Brochure).

A Phase II, parallel-group, dose-finding trial (WA21493) evaluated ocrelizumab compared with placebo and Avonex® (interferon-β1a) in patients with RRMS for up to 96 weeks. In this study, both the 600-mg and 1000-mg dose were administered over 4 cycles. After the first cycle, during which only the 600-mg dose was divided in half and given over a 15-day interval, subsequent cycles involved administration as a single, undivided dose. Doses were administered over approximately 240 minutes. The infusion schedule in this study shows that, both for the 600- and 1000-mg dose, approximately 400 mg of ocrelizumab were infused within 2 to 2.5 hours. However, in the remaining 1.5 to 2 hours of the infusion, only 200 mg remained to be infused for the lower dose, while in the 1000-mg dose, 600 mg were given within the same timeframe. Based on this infusion schedule, a dose/infusion rate/IRR relationship was not clearly observed.

The lack of dose/infusion rate/IRR relationship based on the current clinical data is supportive of the hypothesis that administration of ocrelizumab over a shorter infusion time should not pose a potential additional risk to patients in terms of increased risk of IRRs, but would help convenience of use and compliance for both patients and healthcare practices. In addition, procedures are in place to further mitigate risk of IRR, such as a pre-treatment schedule and guidance around infusion adjustment, if required.

After the infusion, patients will be followed for safety, per the substudy schedule of activities, to monitor for any effects of the shorter administration.

Appendix 2
Optional Shorter Infusion Substudy (cont.)

OBJECTIVES

The primary objective of this study is to evaluate the rate and severity of infusion-related reactions (IRRs) of the ocrelizumab 600-mg infusion administered over the course of 2 hours, instead of the currently approved duration of 3.5 hours, in patients with MS who have had prior treatment with ocrelizumab in MN30035 (CHORDS), as measured by the rate and frequency of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) Grade 3 and 4 IRRs.

STUDY DESIGN

This is an open-label, non-randomized substudy to MN30035 designed to evaluate the safety and tolerability of ocrelizumab infused over a shorter time period than the approved administration rate. Patients who complete their Week 72 ocrelizumab infusion and do not experience any serious IRR (see Section 5.2.2 for seriousness criteria) throughout the main study will be eligible to enroll in this optional substudy and receive one additional shorter infusion of ocrelizumab at the Week 96 visit.

Premedication in the substudy will be administered per the main study methods (Section 4.3.3). Ocrelizumab will then be administered as a single 600-mg dose at a shorter infusion rate (i.e., over the course of approximately 2 hours instead of 3.5 hours) than in the main study.

Ocrelizumab infusion rate will be slowed and/or stopped if a patient experiences a Grade 3 or higher IRR or other serious adverse event.

Patients who received ocrelizumab at a shorter infusion rate at the Week 96 visit will return for a substudy follow-up visit approximately 30 days after treatment.

The end of the treatment period in the substudy is defined as the date when the last patient in the substudy completes the substudy follow-up visit (Week 100).

Planned Total Sample Size

This substudy will enroll approximately 100 patients from MN30035 who did not experience any serious IRR throughout the main study.

OUTCOME MEASURES

Safety Outcome Measures

- *Rate and frequency of Grade 3 or 4 IRRs with onset on or after the shorter ocrelizumab infusion at Week 96 and at the substudy follow-up*
- *Changes in physical findings and vital signs with onset on or after the shorter ocrelizumab infusion at Week 96 and at the substudy follow-up*

Appendix 2
Optional Shorter Infusion Substudy (cont.)

SAFETY PLAN

Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the substudy. Patient safety will be ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically before and during their participation in this substudy. Safety evaluations will consist of medical interviews, recording of adverse events, and physical examinations. Adverse events will be graded according to NCI CTCAE v4.0.

Administration of ocrelizumab will be performed in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member. All adverse events and serious adverse events will be recorded during the substudy for at least 30 days after treatment (i.e., the substudy follow-up period). Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v4.0. Safety assessments will be conducted per the substudy schedule of activities.

The identified and potential safety issues anticipated in this substudy, including IRRs, are reported in the Ocrelizumab Investigator's Brochure. Guidelines for the management of patients who experience specific adverse events are also included in the Ocrelizumab Investigator's Brochure.

PATIENT SELECTION CRITERIA

Inclusion Criteria

Patients must continue to meet the following:

- *Actively enrolled in the main study*
- *Completed Week 72 infusion*
- *Signed substudy Informed Consent Form prior to the Week 96 infusion*
- *Able to comply with the substudy protocol, in the investigator's judgment*

Exclusion Criteria

Patients who become ineligible for any reason in the main study, in addition to the following:

- *Any documented serious IRR at any time during the main study*

TRIAL DRUG

Dosage, Administration, and Storage

Patients will receive 600-mg IV ocrelizumab per a shorter infusion protocol (see Table 1).

Appendix 2
Optional Shorter Infusion Substudy (cont.)

Table 1: Infusion Rates for 600-mg Ocrelizumab Shorter Dose

Time (min)	*Infusion rate (mL/hr)*	*Infusion rate (mg/hr)*	*Max Dose per Interval (mg)*	*Cumulative Dose (mg)*
0–15	*100*	*120*	*30*	*30*
15–30	*200*	*240*	*60*	*90*
30–60	*250*	*300*	*150*	*240*
60–90	*300*	*360*	*180*	*420*
90–120	*300*	*360*	*180*	*600*

Infusion time: 120 min.
Preparation per U.S. label: 600 mg ocrelizumab/500 mL normal saline toward a drug concentration of approximately 1.2 mg/mL.

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

To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent steroid), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each ocrelizumab infusion.

It is also strongly recommended that the infusion is accompanied by prophylactic treatment with an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to the start of an infusion to reduce potential IRRs.

Since transient hypotension may occur during ocrelizumab infusion, the investigator may wish to withhold anti-hypertensive medications 12 hours prior to ocrelizumab infusion.

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.

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.

See the Ocrelizumab IB for detailed instructions on drug preparation, storage, and approved administration.

Dosage Modification

Unless an IRR occurs necessitating discontinuation, the entire contents of the infusion bag must be administered to the patient.

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

- *Life-threating IRR or serious hypersensitivity reaction*
- *Active hepatitis B infection*
- *Progressive multifocal leukoencephalopathy (PML)*
- *Active tuberculosis, either new onset or reactivation*

SUBSTUDY ASSESSMENTS

Substudy assessments will be performed according to the schedule of activities in Table 3.

Informed Consent Forms and Screening Log

Written informed consent for participation in the substudy must be obtained before performing any substudy-related procedures.

Physical Examinations

A limited physical examination will be conducted at the substudy treatment visit. Any abnormality identified prior to treatment administration in the substudy should be recorded on the eCRF. New or worsened clinically significant abnormalities after treatment administration should be recorded as adverse events, if appropriate.

Vital Signs

Vital signs will include measurements of heart rate, temperature, and systolic and diastolic blood pressure.

Appendix 2
Optional Shorter Infusion Substudy (cont.)

Vital signs should be taken approximately 45 minutes prior to premedication. In addition, vital signs should be obtained prior to the ocrelizumab infusion and then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

SUBSTUDY FOLLOW-UP

Patients should have substudy follow-up 30 days after the date of the last infusion of ocrelizumab in this substudy, consisting of one clinic visit. After 30 days, patients may continue to be followed per the main study safety follow-up if they do not continue onto commercial ocrelizumab.

STATISTICAL METHODS

Safety Analyses

Safety analyses will include all patients who received any amount of study treatment in the substudy.

Safety will be summarized using descriptive statistics. Continuous variables will be summarized using n (sample size), mean, standard deviation, median, minimum, and maximum. Frequency distributions (patient counts and associated percentages) will be used to summarize categorical variables. When applicable, 95% confidence intervals (CIs) will be provided for the mean and proportion. The Clopper and Pearson method will be used to calculate exact CIs for proportion when applicable.

All adverse events occurring on or after treatment will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for individual adverse events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from the study due to an adverse event, adverse events leading to infusion adjustment, and treatment-related adverse events will be summarized. In addition, all serious adverse events and deaths will be listed.

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

Ocrelizumab exposure will be summarized, including rate of infusion and dosage.

Appendix 2
Optional Shorter Infusion Substudy (cont.)

Handling of Missing Data

For adverse events with a missing onset date, data will be imputed.

Missing assessments for continuous variables, such as physical examinations and vital signs, will not be imputed.

Determination of Sample Size

Based on the sample size of 100 patients used for analysis, the 95% CIs for some assumed Grade 3 or 4 IRRs are provided in Table 2.

Table 2: Determination of Substudy Sample Size

Number of Patients with Grade 3 or 4 IRRs	*Grade 3 or 4 IRRs (%) (N=100)*	*95% CIs for Grade 3 or 4 IRRs (%)*
1	*1.00*	*(0.03, 5.45)*
2	*2.00*	*(0.24, 7.04)*
3	*3.00*	*(0.62, 8.52)*
4	*4.00*	*(1.10, 9.93)*
5	*5.00*	*(1.64, 11.28)*
6	*6.00*	*(2.23, 12.60)*
7	*7.00*	*(2.86, 13.89)*

The 95% CIs for the IRR (%) are calculated based on the Clopper and Pearson method.

Appendix 2
Optional Shorter Infusion Substudy (cont.)

Table 3: Substudy Schedule of Activities

	Week 96 Treatment Visit (±14 days)	***Substudy Follow-up Visit (30±14 days later)*** [a]
Informed consent [b]	*x*	
Review inclusion and exclusion criteria	*x*	
Physical examination [c]	*x*	*x*
Weight	*x*	
Vital signs [d]	*x*	*x*
Brain MRI [e]	*x*	
Pregnancy test [f]	*x*	
Adverse event assessment [g]	*x*	*x*
Concomitant treatment review	*x*	*x* [h]
Methylprednisolone and antihistamine premedication [i]	*x*	
Ocrelizumab administration	*x*	

eCRF=electronic case report form; IRR=infusion-related reaction; IV=intravenous; MRI=magnetic resonance imaging; PML=progressive multifocal leukoencephalopathy.

[a] *Conducted 30 days after the shorter infusion with ocrelizumab.*

[b] *Written informed consent will be obtained from all patients in order to be eligible for the study and prior to any study procedures.*

[c] *A limited physical examination may be conducted. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate*

[d] *Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and temperature. Vital signs should be taken approximately 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then approximately every 15 minutes for the first hour, followed by approximately every 30 minutes until 1 hour after the end of the infusion.*

[e] *Should only be done if PML is suspected, and should not be done in addition to an MRI at Week 96 conducted in the main study. If needed, should be done pre-dose.*

[f] *Pregnancy test should not be done in addition to the pregnancy test at Week 96 conducted in the main study. If needed, should be done pre-dose.*

[g] *After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, related serious adverse events must be collected and reported regardless of the time elapsed from the study drug administration, even if the substudy has been closed. Unrelated serious adverse events must be collected and reported during the substudy and substudy follow-up. Non-serious adverse events have to be reported until the end of substudy follow-up.*

[h] *Medications used after treatment discontinuation should be recorded during substudy follow-up.*

[i] *All patients must receive prophylactic treatment with 100 mg methylprednisolone (or equivalent), to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes before each infusion of ocrelizumab. Prophylactic treatment with an analgesic/antipyretic (e.g., 1 g acetaminophen) is strongly recommended 30–60 minutes prior to the start of ocrelizumab infusion to reduce the risk of IRRs.*

Appendix 3
Expanded Disability Status Scale (EDSS)

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+).

Appendix 3
Expanded Disability Status Scale (EDSS) (cont.)

- ❑ 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.

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*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 4
2010 Revised McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical (attacks)	Lesions	Additional Criteria to Make Diagnosis
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratorial, spinal cord); OR • Await further clinical attack implicating a different CNS site
1	Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR • A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; OR • Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR • Await further clinical attack implicating a different CNS site AND Dissemination in time, demonstrated by • Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; OR • A new T2 and/or contrast-enhancing lesions(s) on follow-up MIR, irrespective of its timing; OR • Await a second clinical attack

Appendix 4
2010 Revised McDonald Diagnostic Criteria for Multiple Sclerosis (cont.)

Clinical (attacks)	Lesions	Additional Criteria to Make Diagnosis
0 (progression from onset)		One year of disease progression (retrospective or prospective) AND at least 2 out of 3 criteria: • Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; • Dissemination in space in the spinal cord based on ≥2 T2 lesions; OR • Positive CSF
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS

CNS = central nervous system; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.

Sources:
http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Paper-TipSheet_-2010-Revisions-to-the-McDonald-Criteria-for-the-Diagnosis-of-MS.pdf

Polman et al. 2011.

Appendix 5
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 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

ACTION STEPS IF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IS SUSPECTED:

- If the clinical presentation is suggestive of PML, further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of JC virus (JCV) DNA using a validated assay should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

MRI ASSESSMENT

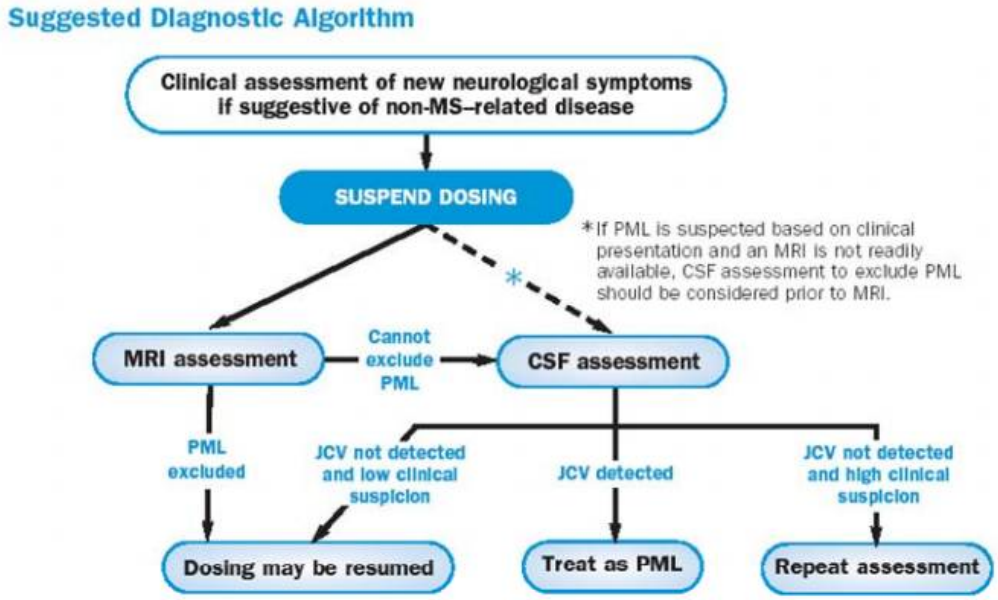
- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive 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 for differences in lesion characteristics that may help differentiate between PML and multiple sclerosis [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.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Figure 1 Diagnostic Algorithm for PML



CSF = cerebrospinal fluid; JCV = JC virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Table 1

Clinical Signs and Symptoms Typical of MS and PML*		
Onset	**MS** **Acute**	**PML** **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)

Source: Kappos et al. 2007.

Appendix 6
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal chord, in white and possibly gray matter	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; 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 T2-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 T1-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 T2-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

Source: Yousry et al. 2006.