

Official Title: A Phase IIIb, Open-Label Study to Evaluate the Safety and Tolerability of Shorter Infusions of Ocrelizumab in Patients With Primary Progressive and Relapsing Multiple Sclerosis

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PROTOCOL

TITLE: A PHASE IIIB, OPEN-LABEL STUDY TO EVALUATE
THE SAFETY AND TOLERABILITY OF SHORTER
INFUSIONS OF OCRELIZUMAB IN PATIENTS WITH
PRIMARY PROGRESSIVE AND RELAPSING MULTIPLE
SCLEROSIS

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PROTOCOL ACCEPTANCE FORM

TITLE: AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY
AND TOLERABILITY OF SHORTER INFUSIONS OF
OCRELIZUMAB IN PATIENTS WITH PRIMARY
PROGRESSIVE AND RELAPSING MULTIPLE
SCLEROSIS

PROTOCOL NUMBER: ML40638

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TEST PRODUCT: Ocrelizumab (RO4964913)

MEDICAL MONITOR: [REDACTED] M.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 of the signed form to the contact provided below.

[REDACTED]
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

PROTOCOL SYNOPSIS

TITLE: AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SHORTER INFUSIONS OF OCRELIZUMAB IN PATIENTS WITH PRIMARY PROGRESSIVE AND RELAPSING MULTIPLE SCLEROSIS

PROTOCOL NUMBER: ML40638

VERSION NUMBER: 1

EUDRACT NUMBER: Not applicable

IND NUMBER: 100593

TEST PRODUCT: Ocrelizumab (RO4964913)

PHASE: Phase IIIb

INDICATION: PPMS and RMS

SPONSOR: Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety of administering ocrelizumab per a shorter infusion protocol (i.e., shorter than the currently approved U.S. labeling rate) in patients with primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
<ul style="list-style-type: none">To evaluate the occurrence of severe IRRs with ocrelizumab 600 mg IV administered over the course of 2 hours	<ul style="list-style-type: none">Rate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 600 mg shorter infusion
Secondary Objective	Corresponding Endpoints
<ul style="list-style-type: none">To evaluate the occurrence of overall IRRs with ocrelizumab administered per a shorter infusion protocol for both cohorts	<ul style="list-style-type: none">Rate and frequency of NCI CTCAE v4.0 Grade 1–4 IRRs in patients who receive the shorter infusion for both cohortsRate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 300 mg shorter infusion

IRR=infusion-related reaction; IV=intravenous; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

Study Design

Description of Study

This study is an open-label, non-randomized study to evaluate rate and severity of infusion-related reactions (IRRs) of ocrelizumab infused over a shorter time period than the approved administration rate in patients with PPMS or RMS in the U.S. The study will have 2 cohorts:

- Cohort 1 will examine the effect of administering ocrelizumab per a shorter infusion protocol for Dose 2 or Dose 3 (Week 24 or 48 from the initial infusion). This cohort will consist of patients who have already received one or two doses of ocrelizumab according to the approved infusion protocol (i.e., per the currently U.S. label) and have reported no serious IRRs and who will then receive the next infusion of ocrelizumab at a higher rate in order to deliver 600 mg over the course of approximately 2 hours.
- Cohort 2 will examine the effect of administering ocrelizumab per a shorter infusion protocol for the second infusion of Dose 1. This cohort will consist of ocrelizumab-naïve patients who, after receiving Infusion 1/Dose 1 of ocrelizumab at the approved rate (300 mg over approximately 2.5 hours or longer) have no reported serious IRRs, will then receive the second 300-mg shorter infusion over approximately 1.5 hours.

All patients will have two safety follow-up telephone calls: the first within 24 hours of the ocrelizumab infusion and the second 30 days after their last ocrelizumab dose.

Number of Patients

Approximately 150 patients with PPMS and RMS at approximately 5 study sites in the U.S. who fulfill the eligibility criteria listed below may participate in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Eligible to receive ocrelizumab per the United States Package Insert (USPI)
- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a diagnosis of PPMS or RMS, confirmed per the revised 2017 McDonald criteria (Thompson et al. 2017)
- Expanded Disability Status Scale (EDSS) score of 0 to 6.5, inclusive
EDSS does not need to be performed if results within 6 months are available.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study treatment (per the USPI)

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Experienced serious IRR(s) (see Section 5.2.2 for seriousness criteria) for those who have previously received ocrelizumab
- History of life-threatening infusion reaction to ocrelizumab

- Known presence of other neurological disorders, including but not limited to, the following:
 - 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 central nervous system 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 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
- 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 alcohol or drug abuse within 24 weeks prior to enrollment
- Receipt of a live vaccine within 6 weeks prior to enrollment
- Systemic corticosteroid therapy within 4 weeks prior to enrollment
 - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- 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 other than ocrelizumab (e.g., rituximab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental
- Any of the following abnormal laboratory results per local laboratory standards and investigator assessment. Results should be available per medical history within 6 months prior to the study; otherwise, assessments should be repeated prior to Day 1:

Lymphocyte count

CD4 count

AST or ALT

Platelet count

Total neutrophil count

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)

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The last scheduled visit is 30 days after the last dose.

Length of Study

The total length of the study for both cohorts is up to approximately 8 weeks.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is ocrelizumab, which is approved for the treatment of PPMS and RMS.

Non-Investigational Medicinal Products

Premedicate with slow IV infusion of 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.

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered 30–60 minutes before ocrelizumab infusion to further reduce the frequency and severity of IRRs.

Statistical Methods

Primary Analysis

For the primary analysis, the number and proportion of patients who experience Grade 3 or 4 IRRs following the 600 mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson confidence interval (CI) of the proportion.

Determination of Sample Size

This study will enroll approximately 150 patients.

Based on the sample size of 100 patients in Cohort 1 and 50 patients in Cohort 2, the 95% CIs for some assumed Grade 3 or 4 IRRs are provided in the Determination of Sample Size table (Table 7).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CI	confidence interval
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
Ig	immunoglobulin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IxRS	Interactive Voice/Web Response System
LLN	lower limit of normal
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI	National Cancer Institute
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
RA	rheumatoid arthritis
RMS	relapsing multiple sclerosis
RRMS	relapsing/remitting MS
SPMS	secondary progressive MS
ULN	upper limit of normal
U.S.	United States
USPI	United States Package Insert

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, with approximately 64%–70% of diagnosed patients being women (Goodin 2014). MS is subcategorized into three main phenotypic disease patterns including relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). The term “RMS” (i.e., relapsing multiple sclerosis) applies to those patients with either RRMS or SPMS who continue to suffer relapses.

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).

Ocrelizumab is indicated for the treatment of adult patients with relapsing or primary progressive forms of MS (United States Package Insert [USPI]). See the Ocrelizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is an exploratory, open-label investigation to evaluate the rate and severity of infusion-related reactions (IRRs) of the ocrelizumab 600-mg infusion from the second treatment course onward, over the course of 2 hours instead of the currently approved duration of 3.5 hours. Specifically, this study will explore, for the first time, the effect of a shorter infusion on the rate and severity of IRRs. Different doses of ocrelizumab have been studied over the years in various patient populations, showing consistently that the proportion of reported IRRs is dose-dependent. However, there is no direct evidence on whether a shorter infusion time would pose an additional safety risk to patients.

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.

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- β 1a) 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.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety of administering ocrelizumab per a shorter infusion protocol (i.e., shorter than the currently approved U.S. labeling rate) in patients with PPMS and RMS. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
<ul style="list-style-type: none">To evaluate the occurrence of severe IRRs with ocrelizumab 600 mg IV administered over the course of 2 hours	<ul style="list-style-type: none">Rate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 600 mg shorter infusion
Secondary Objective	Corresponding Endpoints
<ul style="list-style-type: none">To evaluate the occurrence of overall IRRs with ocrelizumab administered per a shorter infusion protocol for both cohorts	<ul style="list-style-type: none">Rate and frequency of NCI CTCAE v4.0 Grade 1–4 IRRs in patients who receive the shorter infusion for both cohortsRate and frequency of NCI CTCAE v4.0 Grade 3 and 4 IRRs in patients who receive the 300 mg shorter infusion

IRR=infusion-related reaction; IV=intravenous; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

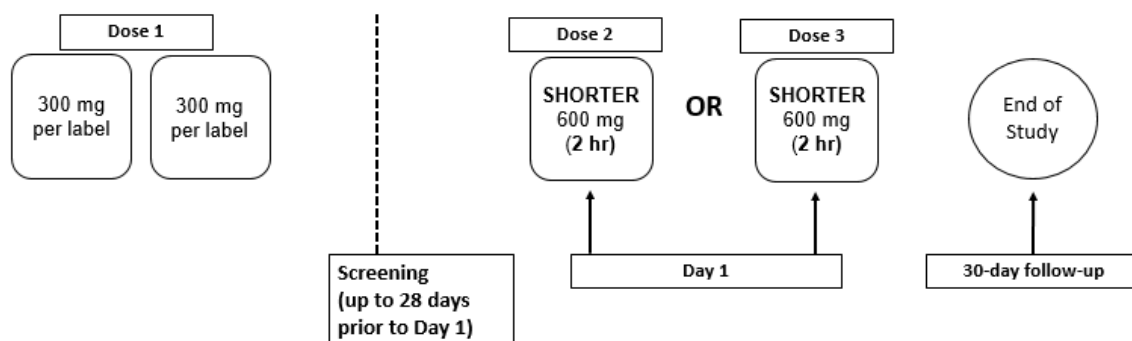
This study is an open-label, non-randomized study to evaluate rate and severity of IRRs of ocrelizumab infused over a shorter time period than the approved administration rate in patients with PPMS or RMS in the U.S. The study will have 2 cohorts:

- Cohort 1 will examine the effect of administering ocrelizumab per a shorter infusion protocol for Dose 2 or Dose 3 (Week 24 or 48 from the initial infusion). This cohort will consist of patients who have already received one or two doses of ocrelizumab according to the approved infusion protocol (i.e., per the currently U.S. label) and have reported no serious IRRs and who will then receive the next infusion of ocrelizumab at a higher rate in order to deliver 600 mg over the course of approximately 2 hours.
- Cohort 2 will examine the effect of administering ocrelizumab per a shorter infusion protocol for the second infusion of Dose 1. This cohort will consist of ocrelizumab-naïve patients who, after receiving Infusion 1/Dose 1 of ocrelizumab at the approved rate (300 mg over approximately 2.5 hours or longer) have no reported serious IRRs, will then receive the second 300-mg shorter infusion over approximately 1.5 hours.

All patients will have two safety follow-up telephone calls: the first within 24 hours of the ocrelizumab infusion and the second 30 days after their last ocrelizumab dose.

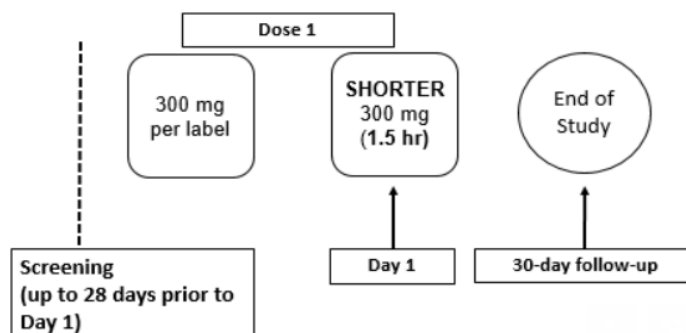
[Figures 1](#) and [2](#) present the study overview by Cohort 1 and Cohort 2. A schedule of activities is provided in [Appendix 1](#) for Cohort 1 and [Appendix 2](#) for Cohort 2.

Figure 1 Study Schema: Cohort 1



Note: For Cohort 1, Dose 1 will be received prior to study enrollment per standard of care. Day 1 may occur at Week 24 or 48, depending on the previous treatment cycle.

Figure 2 Study Schema: Cohort 2



Note: For Cohort 2, Day 1 of Dose 1 is per standard of care.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The last scheduled visit is 30 days after the last dose.

The total length of the study for both cohorts is up to approximately 8 weeks.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ocrelizumab Dose and Schedule

Although IRRs are the most frequently reported adverse event for ocrelizumab, the majority of these events occur with the first infusion of the first dose and decrease over subsequent infusions. The majority of IRRs are mild to moderate (Grade 1 or 2) in severity. Among patients with MS who did not experience an IRR with the first infusion

of ocrelizumab in clinical trials (OPERA I [Study WA21092], OPERA II [WA21093], and Oratorio [Study WA25046]), <20% had subsequent IRRs (Hauser et al. 2018). The higher cumulative dose rate of the 1000-mg infusion in the Phase II Study WA21493 provides relevant information suggesting that a shorter infusion can be administered in this population with acceptable safety outcomes.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 150 patients with PPMS and RMS at approximately 5 study sites in the U.S. who fulfill the eligibility criteria listed below may participate in this study.

4.1.1 Inclusion Criteria

- Signed Informed Consent Form
- Eligible to receive ocrelizumab per the USPI
- Able to comply with the study protocol, in the investigator's judgment
- Age 18–55 years, inclusive
- Have a diagnosis of PPMS or RMS, confirmed per the revised 2017 McDonald criteria (Thompson et al. 2017)
- Expanded Disability Status Scale (EDSS) score of 0 to 6.5, inclusive
 - EDSS does not need to be performed if results within 6 months are available.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study treatment (per the USPI)
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

- Experienced serious IRR(s) (see Section 5.2.2 for seriousness criteria) for those who have previously received ocrelizumab
- History of life-threatening infusion reaction to ocrelizumab
- Known presence of other neurological disorders, including but not limited to, the following:
 - 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 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
- 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 alcohol or drug abuse within 24 weeks prior to enrollment
- Receipt of a live vaccine within 6 weeks prior to enrollment
- Systemic corticosteroid therapy within 4 weeks prior to enrollment
 - There should be 4 weeks from last dose of systemic corticosteroid therapy prior to first infusion.
- 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 other than ocrelizumab (e.g., rituximab, atacicept, belimumab, or ofatumumab)
- Treatment with a drug that is experimental
- Any of the following abnormal laboratory results per local laboratory standards and investigator assessment. Results should be available per medical history within 6 months prior to the study; otherwise, assessments should be repeated prior to Day 1:
 - Lymphocyte count
 - CD4 count
 - AST or ALT
 - Platelet count
 - Total neutrophil count
 - 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)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study in which all patients will receive ocrelizumab. Patients meeting the eligibility criteria for the study will be enrolled into either Cohort 1 or Cohort 2.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab, which is approved for the treatment of PPMS and RMS.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab

Ocrelizumab is 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 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.

Administer the diluted infusion solution through a dedicated line using an infusion set with a 0.2 or 0.22 micron in-line filter.

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 **Study Treatment Dosage, Administration, and Compliance**

The treatment regimen is summarized in Section 3.1.

Patients in Cohort 1 will receive 600-mg IV ocrelizumab per a shorter infusion protocol for Dose 2 or Dose 3. After their infusion, patients in Cohort 1 will have a brief telephone interview within 24 hours of the infusion to assess patient status. Patients will then continue to Safety Follow-up 30 days after their last dose of ocrelizumab and complete the study.

Patients in Cohort 2 will receive Dose 1 of ocrelizumab as 2 split 300-mg IV infusions 14 days apart. The first infusion will be administered per the U.S. label; the second infusion will be administered per a shorter infusion protocol. Patients will have a telephone call within 24 hours of infusion and then continue to Safety Follow-up 30 days after their last dose and complete the study.

For shorter infusion rates, see Table 2 and Table 3 below.

Table 2 Shorter Infusion Rates for 600-mg Ocrelizumab (Cohort 1)

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.

Table 3 Shorter Infusion Rates for 300-mg Ocrelizumab (Cohort 2, Infusion 2 of Dose 1)

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	100	120	30	60
30–60	200	240	120	180
60–90	200	240	120	300

Infusion time: 90 min.

Preparation per U.S. label: 300 mg ocrelizumab/250 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.

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 approved administration.

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 4.6.1.

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

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.4.

4.3.3 Mandatory Premedication: Methylprednisolone and Antihistaminic Drug

Premedicate with slow IV infusion of 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 reported as adverse events on the Adverse Event eCRF page. Adverse events associated with an overdose or incorrect administration of methylprednisolone or antihistamine should be recorded as "Overdose or Incorrect Administration of Methylprednisolone or Antihistamine" on the Adverse Event eCRF as the primary adverse event without the signs and symptoms associated with it.

4.3.4 Other Prophylactic Treatment

The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered 30–60 minutes before ocrelizumab infusion 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) may be provided by the Sponsor where required by patient/site. The study site will acknowledge receipt of IMPs supplied by the Sponsor, 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 be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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 or in an IxRS, as required.

4.3.6 Continued Access to Ocrelizumab

Ocrelizumab is commercially available in the U.S. where this study is being conducted.

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

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Maintenance therapy

- 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).

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H₂-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2 -adrenergic agonists).

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

The schedule of activities to be performed during the study is provided in [Appendix 1](#) for Cohort 1 and [Appendix 2](#) for Cohort 2. All activities must be performed and documented for each patient.

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 (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to

record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 4 weeks prior to initiation of study treatment will be recorded.

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

4.5.3 Physical Examinations

A physical examination per standard of care will be conducted at the screening visit. Any abnormality identified at baseline should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

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

4.5.4 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.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Samples for the laboratory tests will be collected on the days indicated in the schedule of activities.

- Hematology: CBC, including CD19, per standard of care

- Pregnancy test
 - On infusion visits, a urine pregnancy test must be performed prior to premedication in all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Ocrelizumab must be withheld until pregnancy status is confirmed.

4.5.6 Safety Follow-up Period

Patients who receive ocrelizumab in this study or who discontinue from treatment or the study early, should enter the Safety Follow-up Period and be assessed 30 days counting from the date of their last ocrelizumab infusion via telephone.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Immediately stop and permanently discontinue ocrelizumab if there are signs of a life-threatening or disabling infusion reaction
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy

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

4.6.2 Patient Discontinuation from Study

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
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab is not approved at the shorter infusion rate. The safety plan for patients in this study is based on clinical experience with ocrelizumab in completed and ongoing studies. The anticipated important safety risks for ocrelizumab are outlined below. Please refer to the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

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

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 lower limit of normal (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).

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 5](#) for guidance for diagnosis of PML. Please 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. Please 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.

5.1.3.3 Management of Patients Who Experience Adverse Events

Guidelines for management of specific adverse events are outlined in [Table 4](#).

Additional guidelines are provided in the subsections below.

5.1.3.4 Dose Modifications

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare patients, ocrelizumab treatment may need to be discontinued. Guidance is provided in [Section 5.1.3.3](#).

5.1.3.5 Management Guidelines

Guidelines for management of specific adverse events are outlined in [Table 4](#).

Table 4 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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.
Life-threatening or disabling IRR (e.g., anaphylaxis)	<ul style="list-style-type: none">• 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 [5.2.2](#).

5.2.1 Adverse Events

According to the ICH guideline 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) (see Section [5.3.5.9](#) and Section [5.3.5.10](#) for more information)
- 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 National Cancer Institute Common Terminology Criteria for Adverse Events [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 for this study are as follows:

- 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, all adverse events will be reported until 30 days after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

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

Table 5 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 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of 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 6 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	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> 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.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section [5.3.5.1](#)), 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). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event

eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

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 $5\times$ upper limit of normal [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 ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) 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 $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 MS.

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. 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. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of MS, "Multiple Sclerosis Progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

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 Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event, per standard of care.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient 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.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
 - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
 - The patient has not experienced an adverse event.
 - Cholecystectomy for gallstones and diagnostic testing
- 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

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event 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 (defined Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitors: [REDACTED] M.D. (Primary)
 [REDACTED] ([REDACTED] USA)
 [REDACTED] M.D., Ph.D. (Secondary)
 [REDACTED] ([REDACTED], USA)

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 paper Clinical Trial 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 until 30 days 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 paper Clinical Trial 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 serious adverse events that occur > 30 days after the last dose of study treatment 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 30 days 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.

5.4.4 Reporting Requirements for Cases of 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.

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, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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 30 days 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, ECs, 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

6.1 DETERMINATION OF SAMPLE SIZE

This study will enroll approximately 150 patients.

Based on the sample size of 100 patients in Cohort 1 and 50 patients in Cohort 2, the 95% confidence intervals (CIs) for some assumed Grade 3 or 4 IRRs are provided in the table below.

Table 7 Determination of Sample Size

Sample Size	Number of Pts with Grade 3 or 4 IRRs	P (%)	Exact LCL (%)	Exact UCL (%)
50	1	2	0.05	10.65
50	2	4	0.49	13.71
50	3	6	1.25	16.55
50	4	8	2.22	19.23
50	5	10	3.33	21.81
50	6	12	4.53	24.31
50	7	14	5.82	26.74
50	8	16	7.17	29.11
50	9	18	8.58	31.44
100	1	1	0.03	5.45
100	2	2	0.24	7.04
100	3	3	0.62	8.52
100	4	4	1.10	9.93
100	5	5	1.64	11.28
100	6	6	2.23	12.60
100	7	7	2.86	13.89
100	8	8	3.52	15.16
100	9	9	4.20	16.40
150	1	0.67	0.02	3.66
150	2	1.33	0.16	4.73
150	3	2	0.41	5.73
150	4	2.67	0.73	6.69
150	5	3.33	1.09	7.61
150	6	4	1.48	8.50
150	7	4.67	1.90	9.38
150	8	5.33	2.33	10.24
150	9	6	2.78	11.08

IRR=infusion-related reaction; LCL=lower confidence limit; UCL=upper confidence limit based on 95% confidence interval.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, infusion experience, discontinuation, and completion of 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.

6.4 EFFICACY ANALYSES

Not applicable.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment.

For the primary analysis, the number and proportion of patients who experience Grade 3 or 4 IRRs following the 600-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion.

For secondary analyses, the number and proportion of patients who experience Grade 1–4 IRRs following the 600-mg shorter infusion and the number and proportion of patients who experience Grade 3 or 4 IRRs following the 300-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion.

The number and proportion of patients who require slowing, interruption, or stopping of ocrelizumab due to IRRs following the 300-mg or 600-mg shorter infusion will be provided with a 2-sided 95% exact Clopper-Pearson CI of the proportion.

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.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Study data will be collected in an EDC system. The Sponsor will be responsible for the management of all data collected during this study. Ongoing quality review and oversight will be performed. In the event of discrepant data, the Sponsor will request data clarification from the sites, who will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checks to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor'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 be provided access to study specific 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 review and 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 and review, 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 or paper 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. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile 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.

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 (HIPAA) of 1996. 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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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 (see definition of end of study in Section 3.2).

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. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

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 and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests,), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.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: Cohort 1

	Screening (Up to 28 days prior to Day 1)	Treatment Visit (Day 1) ^a	Telephone Call (24 hours after infusion)	Safety Follow-up (Day 30) ^b
Informed consent ^c	x			
Medical history and demographic data ^d	x			
Review inclusion and exclusion criteria	x			
Physical examination ^e	x			
Vital signs ^f		x		
EDSS	(x) ^g			
Hematology	x			
Pregnancy test ^h		x		
Adverse event assessment ⁱ			x	x
Concomitant treatment review	x	x		x ^j
Methylprednisolone and antihistamine premedication ^k		x		
Ocrelizumab administration		x ^l		

eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; IRR=infusion-related reaction; IV=intravenous.

^a Day 1 may occur at Week 24 or 48, depending on the previous treatment cycle.

^b Patients who receive ocrelizumab in this study or who discontinue from treatment or the study early, should enter the Safety Follow-up Period and be assessed 30 days counting from the date of their last ocrelizumab infusion via telephone.

^c Written informed consent will be obtained from all patients in order to be eligible for the study and prior to any study procedures.

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

^e A physical examination may be conducted, per standard of care. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.

Appendix 1 (cont.)

Schedule of Activities: Cohort 1

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- ^f 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.
- ^g EDSS does not need to be performed if results within 6 months are available.
- ^h On infusion visits, a urine pregnancy test must be performed prior to premedication in all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Ocrelizumab must be withheld until pregnancy status is confirmed.
- ⁱ 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 and Safety Follow-up. Non-serious adverse events have to be reported until the end of Safety Follow-up.
- ^j Medications used after treatment discontinuation should be recorded during Safety Follow-up.
- ^k 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.
- ^l Ocrelizumab will be administered as one 600-mg IV infusion over the course of approximately 2 hours (shorter infusion) for Infusion 2 or 3, depending on how many prior doses the patient has received.
-

Appendix 2

Schedule of Activities: Cohort 2

	Screening (Up to 28 days prior to Day 1)	Treatment Visit (Day 15)	Telephone Call (24 hours after infusion)	Safety Follow-up (Day 30) ^a
Informed consent ^b	x			
Medical history and demographic data ^c	x			
Review inclusion and exclusion criteria	x			
Physical examination ^d	x			
Vital signs ^e		x		
EDSS	(x) ^f			
Hematology	x			
Pregnancy test ^g		x		
Adverse event assessment ^h			x	x
Concomitant treatment review	x	x		x ⁱ
Methylprednisolone and antihistamine premedication ^j		x		
Ocrelizumab administration		x ^k		

Appendix 2 (cont.)

Schedule of Activities: Cohort 2

eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; IRR=infusion-related reaction; IV=intravenous.

- ^a Patients who receive ocrelizumab in this study or who discontinue from treatment or the study early, should enter the Safety Follow-up Period and be assessed 30 days counting from the date of their last ocrelizumab infusion via telephone.
 - ^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 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 visit. Demographic data will include age, sex, and self-reported race/ethnicity.
 - ^d A physical examination may be conducted, per standard of care. Any abnormality identified should be recorded on the eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.
 - ^e 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.
 - ^f EDSS does not need to be performed if results within 6 months are available.
 - ^g On infusion visits, a urine pregnancy test must be performed prior to premedication in all women of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Ocrelizumab must be withheld until pregnancy status is confirmed.
 - ^h 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 and Safety Follow-up. Non-serious adverse events have to be reported until the end of Safety Follow-up.
 - ⁱ Medications used after treatment discontinuation should be recorded during Safety Follow-up.
 - ^j 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.
 - ^k Ocrelizumab will be administered as a split infusion for Dose 1: 300-mg IV per standard of care for Infusion 1 and 300-mg IV over the course of approximately 1.5 hours (shorter infusion) for Infusion 2.
-

Appendix 3

2017 Revised McDonald Diagnostic Criteria for Multiple Sclerosis

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

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Table: The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset

Appendix 4

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 5

Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (PML)

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

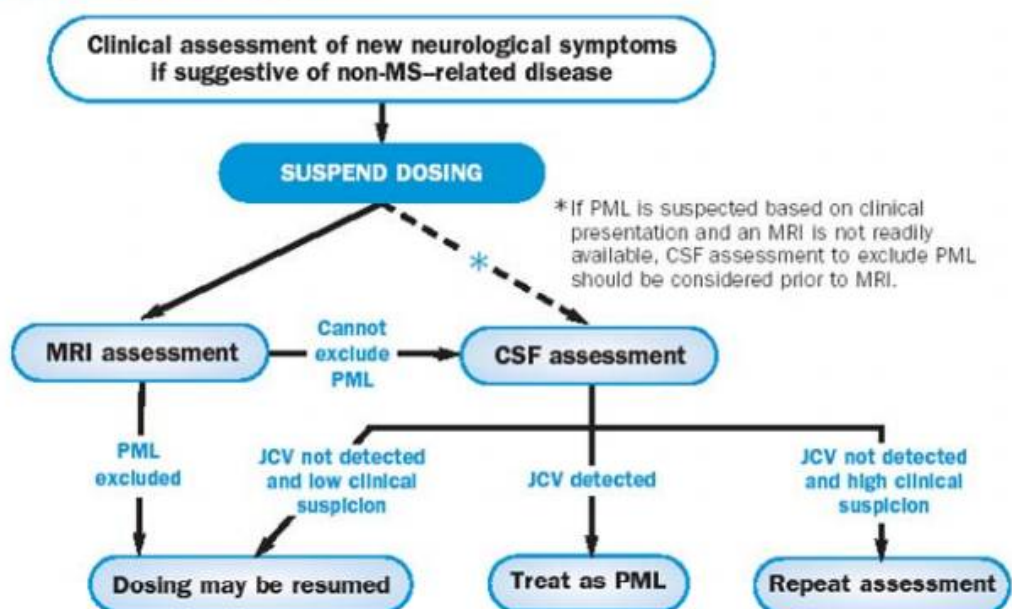
- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Appendix 5

Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (PML).(cont.)

Figure 1 Diagnostic Algorithm for PML

Suggested Diagnostic Algorithm



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*		
	MS Acute	PML Subacute
Onset		
Evolution	<ul style="list-style-type: none"> ➤ Over hours to days ➤ Normally stabilized ➤ Resolve spontaneously even without therapy 	<ul style="list-style-type: none"> ➤ Over weeks ➤ Progressive
Clinical presentation	<ul style="list-style-type: none"> ➤ Diplopia ➤ Paresthesia ➤ Paraparesis ➤ Optic neuritis ➤ Myelopathy 	<ul style="list-style-type: none"> ➤ 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 5

Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (PML).(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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.