PROTOCOL

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, OPEN-LABEL STUDY TO EVALUATE THE EFFECTS OF OCRELIZUMAB ON IMMUNE RESPONSES IN PATIENTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	BN29739
VERSION NUMBER:	8
IND NUMBER:	100,593
NCT NUMBER:	NCT02545868
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
01-Jun-2021 22:36:28	[redacted]	[redacted]
02-Jun-2021 11:41:26		

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
8	See electronic date stamp on title page
7	17 December 2019
6	21 August 2018
5	18 September 2017
4	1 March 2016
3	29 October 2015
2	29 June 2015
1	17 May 2015

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol BN29739 has been amended for the following reasons:

- To clarify that patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for a maximum of 48 weeks after the last infusion of ocrelizumab (OCR). The requirement for continued B-cell monitoring for patients whose B-cells are not repleted (i.e., returned to baseline levels or lower limit of normal, whichever is lower) at the end of the safety follow-up (SFU) period has been removed as no increased safety risk was identified in the OCR clinical development program from Week 48 post-treatment and beyond until B-cell repletion.
- To clarify that after entering SFU and upon treatment initiation with another disease-modifying therapy (DMT), patients will be discontinued from the SFU and from the study. The rationale for this change is that, given the low numbers of patients in the clinical development program who have switched to alternative DMTs, and data consisting of several different DMTs with various treatment durations, the Sponsor considers that such data would not allow any meaningful interpretation and it is unlikely that prolonged data collection would facilitate this. Patients who switch to commercial OCR after entering SFU, will also be discontinued from the SFU and the study.

Changes to the protocol that address the above reasons are summarized below:

- Language has been added to clarify that patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR (Sections 3.1, 4.7.4, and 4.8.2; Appendix 1).
- Text related to continued B-cell monitoring has been removed (Sections 3.1, 3.2, 3.3.5, 4.6.3.1, 4.7.4, 4.7.7, 4.7.8.7, 4.8.2, 5.1.1.5, 5.3.1, 5.4.2.2, 5.6 and 8.5; Figures 1 and 2; Appendices 1 and 2).
- Language has been added to clarify that when patients begin an alternative treatment for multiple sclerosis or start treatment with commercial OCR, they will be discontinued from the SFU and from the study (Sections 3.1, 4.6.3.1, 4.7.4, 4.7.7, 4.8.2; Appendix 1).

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

- Language regarding post-trial access to OCR has been amended to indicate that continued access to OCR will be offered (Section 4.5).
- The safety risks for ocrelizumab have been updated and clarifications have been added to the section. These changes will be or were implemented across the ocrelizumab clinical program for consistency and do not reflect a change in the benefit–risk assessment for ocrelizumab (Section 5.1).

- Guidance for pregnancy reporting has been updated to remove the requirement for reporting within 6 months after the last dose of OCR (Section 5.4.3.1).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.11).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.1).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, OPEN-LABEL STUDY TO EVALUATE THE EFFECTS OF OCRELIZUMAB ON IMMUNE RESPONSES IN PATIENTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, OPEN-LABEL STUDY TO EVALUATE THE EFFECTS OF OCRELIZUMAB ON IMMUNE RESPONSES IN PATIENTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	BN29739
VERSION NUMBER:	8
IND NUMBER:	100,593
NCT NUMBER:	NCT02545868
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	IIIb
INDICATION:	Relapsing forms of multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

The primary efficacy objective for this study is as follows:

- To characterize the humoral immune response (IgG) to tetanus toxoid (TT) adsorbed vaccine in patients with relapsing forms of multiple sclerosis (RMS) who are treated with ocrelizumab (OCR; Group A), compared with that of patients with RMS who are not treated with OCR (Group B).

The secondary efficacy objectives for this study are as follows:

1. To characterize the humoral immune response (IgG) to the 23-valent pneumococcal polysaccharide vaccine (23-PPV) in Group A patients (Groups A1 and A2) compared with Group B patients.
2. To characterize the humoral immune response (IgG) in OCR-treated patients to 23-PPV boosted by a subsequent 13-valent pneumococcal conjugate (13-PCV) vaccine booster (Group A1) compared with unboosted 23-PPV (Group A2).
3. To characterize the humoral immune response (IgG and IgM) to keyhole limpet hemocyanin (KLH) in Group A patients compared with Group B patients.
4. To characterize the humoral immune response (hemagglutination inhibition [HI]) titers) to influenza vaccine in OCR-treated patients (Group A2) patients compared with patients not treated with OCR (Group B).
5. To evaluate the long-term effects of OCR on magnetic resonance imaging (MRI) parameters of disease activity during the Optional Ocrelizumab Extension (OOE) Period of the study.

Group A will be split into Group A1 (patients will receive the booster 13-PCV vaccine), and Group A2 (patients will receive the influenza vaccine).

Safety Objectives

The safety objectives for this study are to collect additional data on the safety of OCR.

Study Design

Description of Study

This Phase IIIb, multicenter, randomized, open-label study is designed to evaluate immune response to vaccines after administration of a dose of OCR (i.e., a dual infusion of OCR 300 mg

on Day 1/Week 1 [Dose 1 Infusion 1] and Day 15/Week 2 [Dose 1 Infusion 2]) in patients with RMS.

Following screening, approximately 100 adult patients will be randomized into Groups A and B (2:1; active:control) to compare responses to immunization. Patients in Group B are to receive immunization with TT-containing adsorbed vaccine, 23-PPV, influenza vaccine, and repeated administration with KLH. Group B patients will not receive OCR but will remain on no MS-specific disease-modifying therapy (DMT) or continue with interferon beta (IFN-β) treatment until optional OCR treatment at the end of the Immunization Study Period.

Patients in Group A are to first receive OCR (Day 1/Week 1 [Dose 1 Infusion 1] and Day 15/Week 2 [Dose 1 Infusion 2]), and 12 weeks post-OCR treatment, are to receive a similar immunization course to Group B. Group A will be further subdivided into two groups to evaluate the effectiveness of a booster 13-PCV vaccination or of influenza vaccination.

For the primary objective and for secondary objectives 1 and 3, Group A (active) will be compared with Group B (control).

To determine the outcomes of secondary objectives 2 and 4, patients in Group A will be split into two groups with 50% of patients in each group (Groups A1 and A2). Patients will be assigned to either Group A1 or A2:

- Group A1 will receive booster 13-PCV (approximately 33 patients)
- Group A2 will receive the influenza vaccine (approximately 33 patients but a minimum of 30 patients).

A minimum of 30 patients will be assigned to Group A2 during the first influenza season. If a minimum of 30 patients (a maximum of 33) are assigned to Group A2 and receive the first year's influenza vaccine, all remaining patients in Group A will be assigned to Group A1 and receive the 13-PCV booster. If less than 30 patients have been assigned to Group A2 during the first influenza season, further patients assigned to Group A2 will have influenza vaccine visits during the subsequent influenza season (i.e., when the next year's vaccine becomes available).

The primary and secondary humoral immunity and immunophenotyping outcomes are to be measured by flow cytometry and quantitative Ig measurements.

Approximately 30–35 centers will participate in the study in the United States/North America. This study consists of up to five study periods:

- Screening Period
- Immunization Study Period

  Group A: Immunization Study Period and OCR treatment starts at Day 1/Week 1. Patients will receive 300 mg of open-label OCR on Day/Week 1 (Dose 1 Infusion 1) and Day 15/Week 2 (Dose 1 Infusion 2). Patients in Group A will be split and be assigned to either Group A1 (booster 13-PCV) or Group A2 (influenza vaccine). At Day 85/Week 12 patients will start to receive immunizations and undergo post-immunization assessments. For all patients in Group A, the Immunization Study Period will end on Day 169/Week 24.

  Group B: Patients will not receive OCR. At Day 1/Week 1, patients will start to receive immunizations and undergo post-immunization assessments. For Group B, the Immunization Study Period will end at Day 84/Week 12.
- Optional OCR Extension Period:
  - **Groups A1 and A2**: Patients who complete the 24–week immunization study period will have the option for retreatment with a single infusion of 600 mg OCR (Dose 2) at Day 169/Week 24 and subsequent single infusions (600 mg OCR) at intervals of 24 weeks provided that he or she meets the OOE retreatment criteria and chooses to receive retreatment.
  - **Group B**: Patients who complete the 12–week immunization study period will have the option to receive OCR in the OOE; the first dose will be administered as two single infusions of 300 mg, on Day 84/Week 12 (Dose 1 Infusion 1) and Day 98/Week 14 (Dose 1 Infusion 2), and subsequent doses will be administered as single 600 mg infusions (Dose 2, Dose 3, etc.) at intervals of 24 weeks provided that he or she meets the OOE retreatment criteria and chooses to receive retreatment. Group B patients

who do not qualify for and/or do not choose treatment with OCR at Week 12 will complete the study at Week 12 and will **not** enter safety follow-up.

Please note that the OOE will continue with all patients who are able to receive OCR as per local guidelines, or unless the Sponsor decides to terminate the OCR program for multiple sclerosis (MS); however, the OOE will not exceed 4 years after the last patient last visit in the Immunization Study Period. *At the end of the OOE, patients may choose to continue on commercially available OCR.*

- Safety Follow-Up (SFU) Period: *Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS or start treatment with commercial OCR, they will be discontinued from the SFU and from the study.*

Number of Patients

This study will enroll approximately 100 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent and to be able to follow the protocol–defined schedule of assessments
- Diagnosis of RMS in accordance with the revised McDonald criteria
- Age 18–55 years, inclusive
- Received at least one previous immunization against TT or tetanus and diphtheria (DT/Td) or tetanus, diphtheria, and acellular pertussis (DTaP/Tdap).
- Expanded Disability Status Scale at screening from 0–5.5 points, inclusive
- Contraception requirements:
  - **For sexually active female patients of reproductive potential,** use of reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, is required):*
    - One primary method of contraception throughout the trial, including the active treatment phase AND for 6 months after the last dose of OCR.

    **Acceptable methods of contraception include one primary (e.g., systemic hormonal contraception or tubal ligation, vasectomy of the male partner) OR a double-barrier method (e.g., latex condom, intrauterine device, vaginal ring or pessary plus spermicide [e.g., foam, vaginal suppository, gel, cream]).*
  - For female patients without reproductive potential:
    - Women may be enrolled if post-menopausal (i.e., spontaneous amenorrhea for 12 months confirmed by a follicle stimulating hormone level $>$ 40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause; or surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

Exclusion Criteria

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

- Contraindications for or intolerance to oral or intravenous (IV) corticosteroids, including methylprednisolone administered IV, according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents

- Known presence of other neurologic disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T–lymphotropic virus-1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders that potentially cause progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren'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

Patients who meet the following criteria related to their general health will be excluded:

- Pregnancy or lactation
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Known hypersensitivity to any component of the TT-containing adsorbed vaccine, including thiomersal (thimerosal in United States)
- History of systematic allergic, neurologic, or other reactions following a previous dose of any TT-containing vaccine
- Known hypersensitivity to any component of any pneumococcal polysaccharide or conjugate vaccine
- Known hypersensitivity to any component of the influenza vaccine
- Allergy to shellfish
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, or gastrointestinal or any other significant disease that may preclude a patient from participating in the study
- Congestive heart failure (New York Heart Association III or 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 major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)
- History of recurrent aspiration pneumonia that required antibiotic therapy
- History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix of the uterus that have been excised and resolved, with documented clean margins on pathology)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study

- History of alcohol or drug abuse within 24 weeks prior to randomization
- History of or currently active primary or secondary immunodeficiency
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or 5 half-lives of the investigational drug, whichever is longer, or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Receipt of any pneumococcal vaccine within 5 years prior to screening
- Previous exposure to KLH
- Previous immunization with any tetanus-containing vaccine within 2 years prior to screening
- If scheduled as per protocol to receive the 2015/2016 vaccine and has already received the 2015/2016 vaccine or if scheduled as per protocol to receive the 2016/2017 vaccine and has already received the 2016/2017 vaccine.
- Receipt of a live vaccine within 6 weeks prior to randomization*

  **Vaccinations before baseline: in rare cases where a live vaccine must be administered by the patient's physician, the screening period may need to be prolonged but cannot exceed 8 weeks.*
- Previous treatment with B-cell targeted therapies (e.g., rituximab, OCR, atacicept, belimumab, or ofatumumab)
- Any previous treatment with alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Any previous treatment with lymphocyte-trafficking blockers (e.g., natalizumab, fingolimod)
- Treatment with IV Ig, plasmapheresis, teriflunomide or dimethyl fumarate, or glatiramer acetate within 12 weeks prior to randomization*
- Systemic corticosteroid therapy within 4 weeks prior to screening**

  ** Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility criteria for the trial. Patients who discontinue their current therapy for non-medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may not receive RMS disease–modifying therapies. Group B patients can continue with IFN-β treatment. If the patient has received teriflunomide he or she may need to go through the accelerated elimination protocol (Genzyme 2013*).

  ***The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for RMS before screening. In addition, for a patient to be eligible, systemic corticosteroids should not have been administered between screening and baseline.*
- Exclusions related to laboratory findings*
  - Positive serum β-human chorionic gonadotropin measured at screening
  - Positive screening tests for hepatitis B (hepatitis B surface antigen positive, or positive hepatitis B core antibody confirmed by a positive viral DNA polymerase chain reaction), or hepatitis C antibody
  - Positive rapid plasma reagin, if confirmed by microhemagglutination assay or fluorescent treponemal antibody absorption test
  - CD4 count $< 300/\mu L$
  - Serum creatinine > 1.4 mg/dL (> 124 μmol/L) for women or > 1.6 mg/dL (> 141 μmol/L) for men
  - AST/SGOT or ALT/SGPT $\geq 2.0 \times$ upper limit of normal
  - Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9$/L)
  - Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)

- ANC $< 1.5 \times 10^3/\mu L$
- Levels of serum IgG 18% below the LLN (for central laboratory: IgG < 4.6 g/L)
- Levels of serum IgM 8% below the LLN (for central laboratory: IgM < 0.37 g/L)

** Retesting before baseline: in rare cases in which the screening laboratory samples are rejected by the central laboratory (example: hemolyzed sample) or the result is not assessable (example: indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria. In such circumstances, the screening period may need to be prolonged but cannot exceed 8 weeks.*

- Based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude TB (e.g., chest X-ray, tuberculin skin or blood test), Lyme disease, HTLV-1–associated myelopathy, AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the investigator.

Eligibility for the Optional Ocrelizumab Extension Period

Only patients who have completed the Immunization Study Period are potentially eligible for the Optional OCR Extension Period. Prior to re-treatment with OCR, patients will be evaluated for the following conditions and laboratory abnormalities.

Re-treatment Criteria

Prior to re-treatment, the following conditions must be met:

- Absence of severe allergic or anaphylactic reaction to a previous OCR infusion
- Absence of any significant or uncontrolled medical condition or treatment–emergent, clinically significant laboratory abnormality
- Absence of active infection (including active TB infection, either new onset or reactivation)*
- ANC $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test**

If any of the conditions are not met prior to re-treatment, further administration of OCR should be suspended until resolved or held indefinitely.

* Patients with active TB infection, either new onset or reactivation, must suspend ocrelizumab treatment for as long as needed to ensure full resolution of the TB infection. These patients should receive medical care in adherence with local/national requirements until complete resolution of the TB infection and should be monitored subsequently as per local medical plans. Upon resolution of the TB infection and based on individual benefit-risk assessments, these patients will have the opportunity to re-start ocrelizumab treatment if it is considered beneficial for them. Otherwise, the treating Investigator can decide to permanently stop ocrelizumab.

*** In the event of pregnancy, the Investigator must counsel the patient as to the risks of continuing with the pregnancy and the possible effects on the fetus. Given there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the completion of pregnancy and breastfeeding. Pregnant and breastfeeding patients should continue to follow the schedule of assessments for the OOE; however, no infusions will occur. If there is a concern with the ability of a pregnant or breastfeeding patient to perform all scheduled assessments, the Investigator must contact the Medical Monitor for further discussion. In the OOE period of the study, re-start of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit/risk discussion between the patient and investigator.*

Length of Study

The treatment period (including OOE) will not exceed 4 years after the last patient last visit (LPLV) in the Immunization Study Period. The last patient last visit in the Safety Follow-Up Period (i.e., 48 weeks after the last dose of OCR) is anticipated to be within 5 years after the LPLV in the Immunization Study Period. However, the end of study is defined as the last patient last visit *in* the *Safety Follow-Up Period*.

End of Study

The end of study is defined as the last patient last visit in the Safety Follow-Up Period.

Outcome Measures

Primary Immunization Outcome Measure

The primary outcome measure is the proportion of patients in Groups A (i.e., combined Groups A1 and A2) and B with a positive response (IgG) to TT vaccine measured 8 weeks after TT vaccine administration.

- For patients with pre-immunization tetanus antibody titers < 0.1 IU/mL, a positive response to the booster immunization is defined as an antibody titer ≥ 0.2 IU/mL measured 8 weeks after immunization. For patients with pre-immunization tetanus antibody titers ≥ 0.1 IU/mL, positive response to the booster immunization is defined as a 4-fold increase in antibody titers compared with pre-vaccination levels measured 8 weeks after immunization. Pre-immunization levels are those obtained immediately prior to administration of a vaccine.

Secondary Outcome Measures

The secondary outcome measures are as follows:

- TT response:
  - The proportion of patients in Groups A (A1 and A2) and B with a positive response (IgG) to TT vaccine measured 4 weeks after TT vaccine administration.
  - The proportion of patients in Groups A (A1 and A2) and B with a 2-fold increase in tetanus antibody titers, or with tetanus antibody titers $\geq$ 0.2 IU/mL, measured 4 weeks after the immunization of patients with pre-immunization tetanus antibody titers $\geq$ 0.1 IU/mL or with pre-immunization tetanus antibody titers $<$ 0.1 IU/mL, respectively.
  - Mean levels of anti-tetanus antibody in patients in Groups A (A1 and A2) and B measured immediately prior to and 4 weeks after a booster TT vaccine.
- Pneumococcal vaccine response:
  - The proportion of patients in Groups A (A1 and A2) and B with positive antibody responses against an individual pneumococcal serotype measured 4 weeks after the 23-PPV (23 serotypes). (A positive response against a serotype is defined as developing a 2-fold increase in antibody level or a $>$ 1 μg/mL rise in level compared with pre-immunization levels. Pre-immunization levels are those obtained immediately prior to receipt of 23-PPV.) Post-immunization levels will be measured 4 and 8 weeks after 23-PPV administration for Groups A1, A2, and B.
  - The proportion of patients in Groups A (A1 and A2) and B with a positive response against at least 2 out of 23 pneumococcal antibody serotypes measured 4 weeks after administration of 23-PPV vaccine.
  - The proportion of patients in Groups A (A1 and A2) and B with positive responses against at least 50% of the serotypes ($\geq$ 12 of 23) measured 4 weeks after administration of 23-PPV vaccine.
  - Mean levels of anti-pneumococcal serotype-specific antibody in patients in Groups A (A1 and A2) and B measured immediately prior to and 4 and 8 weeks (which is 4 weeks after Group A1 patients received the 13-PCV booster) after administration of 23-PPV vaccine.

- KLH response:
  - Mean levels of anti-KLH antibody (IgG and IgM) in patients in Groups A (A1 and A2) and B measured immediately prior to the first administration of KLH and 4 weeks after the last administration of KLH.
  - Mean levels of anti KLH antibodies (IgG and IgM) in patients in Groups A (A1 and A2) and B measured over time at 4, 8, and 12 weeks after first KLH administration.
- Strain-specific influenza vaccine response in Groups A2 and B:
  - Proportion of patients who achieve seroprotection defined as specific HI titers $>$ 40 at 4 weeks post-immunization
  - Proportion of patients who achieve a 2-fold increase in specific HI titers at 4 weeks post-immunization
  - Proportion of patients who achieve a 4-fold increase in specific HI titers at 4 weeks post-immunization
  - Proportion of patients with seroconversion (i.e., a pre-vaccination antibody titer $<$ 10 and a post-vaccination HI titer $>$ 40);
  - Strain–specific geometric mean titers (GMTs) at baseline and at 4 weeks post-vaccination
  - Strain–specific GMT ratio (post-vaccination:pre-vaccination)
- MRI assessments to evaluate the long-term effects of OCR on MRI parameters of disease activity during the OOE Period.

Immunophenotyping Outcome Measures

The humoral and cellular immunity outcome measures in this study are as follows:

- Flow cytometry, which will include (but is not limited to) the following cells:
  - Total B cells (CD19 positive)
  - B-cell subsets, e.g., memory B cells, naïve B cells, plasma cells
  - Total T cells (CD3 positive)
  - T helper cells (CD3 positive, CD4 positive)
  - Cytotoxic T lymphocytes (TCTL; CD3 positive, CD8 positive)
  - Natural killer cells (CD3 negative, CD16/56 positive)
- Quantitative Ig: Ig levels (including total Ig, IgG, IgG subtypes, IgM, and IgA)

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Vital signs*, hematologic laboratory tests, anti-drug antibody formation, physical and neurological examinations, and the incidence and severity of adverse events associated with OCR and study immunizations.

  **To monitor infusion-related reactions* (IRRs)*, vital signs will be obtained immediately pre-infusion, every 15 (±5) minutes for the first hour during the infusion, every 30 (±5) minutes for the remainder of the infusion, and at the end of the infusion on days of OCR administration.*

<u>Investigational Medicinal Products</u>

Test Product (Investigational Drug)

During the Immunization Study Period:

- Patients in Group A will be administered OCR by IV infusion at a dose of 300 mg on Day 1/Week 1 (Dose 1 Infusion 1) and Day 15/Week 2 (Dose 1 Infusion 2).
- Patients in Group B will not receive any OCR.

During the OOE, for patients who meet the criteria for optional OCR treatment:

- Patients from Groups A1 and A2 will be administered OCR by IV infusion at a dose of 600 mg on Day 169/Week 24 (Dose 2) and subsequent 600 mg single infusions with an interval of 24 weeks (minimum interval of 22 weeks).
- Patients from Group B will be administered OCR by IV infusion at a dose of 300 mg on Day 84/Weeks 12 (Dose 1 Infusion 1) and Day 98/Week 14 (Dose 1 Infusion 2) and at a dose of 600 mg on Day 252/Week 36 (Dose 2) and subsequent 600 mg single infusions with an interval of 24 weeks (minimum interval of 22 weeks).

Mandatory premedication is required prior to any infusion with OCR.

Non-Investigational Medicinal Products

Premedication: Premedication is mandatory with methylprednisolone 100 mg IV 30 minutes prior to each infusion of OCR, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes prior to each infusion of OCR. In the rare case when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative steroid should be used as premedication prior to the infusion.

Pre-infusion treatment with an oral analgesic/antipyretic (e.g., acetaminophen) 30–60 minutes prior to each infusion of OCR is also recommended

Tetanus toxoid: TT vaccine is indicated for the prevention of tetanus. The TT vaccine will be administered as part of the combined adsorbed vaccine with diphtheria (Td/DT) and/or acellular pertussis (DTaP/Tdap). In this study, TT adsorbed vaccine is being used to assess whether OCR affects antibody production to an antigen to which individuals have pre-existing immunity.

- Group A patients will receive a TT-containing absorbed vaccine (0.5 mL) as an intramuscular (IM) injection in the deltoid muscle at Day 85/Week 12.
- Group B patients will receive a TT-containing absorbed vaccine ([0.5 mL) as an IM injection in the deltoid muscle on Day 1/Week 1.

23-PPV: The 23-PPV is indicated for immunization against pneumococcal disease caused by those pneumococcal serotypes included in the vaccine. It has been chosen for this study to assess antibody production for a clinically relevant antigen that is unknown to most individuals. The 23-PPV will be administered in the deltoid muscle as a single IM injection.

- Group A patients will receive the 23-PPV vaccine (0.5 mL) as an IM injection in the deltoid muscle at Day 112/Week 16.
- Group B patients will receive the 23-PPV (0.5 mL) as an IM injection in the deltoid muscle at Day 28/Week 4.

KLH: KLH is a high molecular weight respiratory metalloprotein found in the hemolymph of many mollusks and crustaceans. However, KLH does not have regulatory approval and is not marketed. Therefore, it may be considered an investigational medicinal product (IMP) in some regions. KLH has been used in global clinical trials as a challenge agent to evaluate patient's immune responses to neo-antigen. In this study, KLH will be used to test primary humoral response following B-cell depletion with OCR.

- Group A patients will receive subcutaneously (SC) administered KLH (1 mg) at Day 85/Week 12, Day 112/Week 16, and Day 140/Week 20.
- Group B patients will receive SC administered KLH (1 mg) at Day 1/Week 1, Day 28/Week 4, and Day 56/Week 8.

13-PCV: This study will assess antibody production when administered as 13-PCV booster vaccine after 23-PPV vaccine. The 13-PCV is indicated as active immunization for the prevention of pneumonia and invasive disease caused by 13 *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). It has been chosen for this study to assess antibody production when administered as 13-PCV booster vaccine after 23-PPV vaccine (the response to serotype 6A will not be tested in the assay used in this study). Booster 13-PCV will be administered in the deltoid muscle as a single IM injection.

- Group A1 patients will receive the 13-PCV at Week 20/Day 140. Refer to the label for dosing and administration guidance.

Seasonal Influenza vaccine: The influenza vaccine is indicated for immunization against influenza caused by the influenza strains included in the vaccine. The inactivated (or recombinant) vaccine has been chosen for this study to assess antibody production for a commonly used clinically relevant antigen. .

- Group A2 patients can receive the influenza vaccine at any time between Day 85/Week 12 and Day 140/Week 20.
- Group B patients will receive the influenza vaccine as an IM injection in the deltoid muscle at any time between Day 1/Week 1 and Day 84/Week 12. If a patient needs to receive the influenza vaccine after Week 12, the optional OCR infusion must be delayed.

Statistical Methods

Primary Analysis

The proportion of patients with positive responses to TT vaccine measured 8 weeks after administration of the TT vaccine for Group A and Group B will be assessed.

For patients with pre-immunization tetanus antibody titers < 0.1 IU/mL, a positive response to the booster immunization is defined as an antibody titer ≥ 0.2 IU/mL measured 8 weeks after the immunization. For patients with pre-immunization tetanus antibody titers ≥ 0.1 IU/mL, positive response to the booster immunization is defined as a 4-fold increase in antibody titer measured 8 weeks after the immunization. Pre-vaccination levels are those obtained immediately prior to receipt of a vaccine.

Determination of Sample Size

Approximately 100 patients will be enrolled using a 2:1 randomization ratio into active (Group A) and control (Group B) groups. For the positive response to TT-containing absorbed vaccine measured 8 weeks after the administration of vaccine, if both the control and active (OCR) groups have 70% response rates, the expected half width of the resulting 95% CI of the difference of two response rates is 0.201.

LIST OF ABBREVIATIONS AND DEFINITIONs OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
CDI	confirmed disability improvement
CDP	confirmed disability progression
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMT	disease-modifying therapy
DT	diphtheria and tetanus toxoids
Dtap	diphtheria-tetanus-acellular pertussis
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FSS	Functional System Score
Gd	Gadolinium
GMT	geometric mean titers
HAM	HTLV-1–associated myelopathy
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HepCAb	hepatitis C antibody
HI/HAI	hemagglutination inhibition
HIPAA	Health Insurance Portability and Accountability Act
HTLV-1	human T–lymphotropic virus-1
IB	investigator's brochure
ICH	International Conference on Harmonisation
IFN	Interferon
IM	Intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	Intravenous

Abbreviation	Definition
IxRS	interactive response system
KLH	keyhole limpet hemocyanin
JCV	John Cunningham virus
LLN	lower limit of normal
MAID	multi-analyte immunodetection (assay)
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	Methotrexate
NCI	National Cancer Institute
NK	natural killer
OCR	ocrelizumab
OLE	open-label extension
OOE	optional ocrelizumab extension
PCR	polymerase chain reaction
13-PCV	13-valent pneumococcal conjugate vaccine
PCV	pneumococcal conjugate vaccine
PK	Pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
23-PPV	23-valent pneumococcal polysaccharide vaccine
PPV	pneumococcal polysaccharide vaccine
RA	rheumatoid arthritis
RMS	relapsing forms of multiple sclerosis
RPR	rapid plasma regain
RRMS	relapsing remitting multiple sclerosis
RTX	Rituximab
SC	Subcutaneous
SFU	safety follow-up
TB	tuberculosis
TCTL	cytotoxic lymphocyte T
Td	tetanus-diphtheria
Tdap	tetanus-diphtheria-acellular pertussis
TT	tetanus toxoid
ULN	upper limit of normal

1. BACKGROUND

Ocrelizumab (OCR) is a recombinant humanized monoclonal antibody (mAb) that selectively targets CD20-expressing B cells (Klein et al. 2013).

CD20 is a cell surface antigen found on pre-B cells, mature B cells, and memory B cells but is not expressed on lymphoid stem cells and plasma cells (Stashenko et al. 1980; Loken et al. 1987; Tedder and Engel 1994). While OCR selectively depletes CD20-expressing B cells (Kappos et al. 2011), the capacity of B-cell reconstitution and preexisting humoral immunity are preserved (Martin and Chan 2006; DeLillo et al. 2008). In addition, innate immunity and total T-cell numbers are not affected (clinical study report [CSR] Study WA21493/ACT4422G).

B cells are thought to play an important role in the pathogenesis of multiple sclerosis (MS) by doing the following:

- Presenting auto-antigens and co-stimulatory signals to activate T cells (Constant 1999; Crawford et al. 2006)
- Secreting pro-inflammatory cytokines at greater relative proportions than protective cytokines (Duddy et al. 2007; Bar-Or et al. 2010)
- Producing auto-antibodies that may cause tissue damage and activate macrophages and natural killer (NK) cells (Storch et al. 1998; Genain et al. 1999)
- Creating meningeal lymphoid follicle–like structures, which are linked to microglia activation, local inflammation, and neuronal loss in the nearby cortex (Serafini et al. 2004; Magliozzi et al. 2010)

The precise mechanisms through which OCR exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through the reduction in the number and function of B cells. These changes are thought to be responsible for the consequent improvement of the disease course of MS (Avivi et al. 2013).

Vaccinations against infections are an important part of the management of patients with MS. Exacerbations have been well documented as a consequence of infection, and infectious diseases have been recognized as a complication of the therapies currently employed in the treatment of MS. For example, influenza can cause serious complications and has been shown to be associated with a higher occurrence of exacerbations in patients with MS (De Keyser et al. 1998; Confavreux et al. 2001). Given the effects of OCR on B cells, an impact on immunization responses might be expected (Williamson and Berger 2015). Therefore, it is important to evaluate if patients treated with OCR can mount protective immune responses against clinically relevant vaccines.

Immunization responses in patients on other anti-CD20 B–cell depleting therapies, such as rituximab (RTX) have been studied in rheumatoid arthritis (RA; Bingham et al. 2010). RTX treatment has been shown to differentially affect serum antibody levels, especially

IgM (Edwards et al. 2004; van Vollenhaven et al. 2010). Conversely, levels of IgG specific for infectious antigens, such as tetanus and pneumococcus, have remained stable over multiple treatment courses (Edwards et al. 2004; van Vollenhaven et al. 2010).

The objective of this study is to characterize the effectiveness of vaccination in patients with relapsing MS (RMS) undergoing treatment with OCR in a randomized, parallel-group, open-label trial.

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

1.1.1 Multiple Sclerosis

MS is a chronic, inflammatory, and demyelinating disease of the human CNS, which affects approximately 2.3 million people worldwide, with a the highest prevalence in North America and Europe, at 140 and 108 per 100,000, respectively (Multiple Sclerosis International Federation 2013). Typically, young adults are affected; 70%–80% of patients have an age of onset (i.e., initial clinical presentation to a physician) of between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002). MS is a heterogeneous disorder both pathophysiologically and phenotypically. This variability can be seen, on the basis of clinical course, via magnetic resonance imaging (MRI) scan assessments, and pathological analysis of biopsy and autopsy material (Luccinetti et al. 2000). The disease manifests itself as a variety of neurological deficits attributable to dysfunction of CNS components, such as the spinal cord, brainstem, optic nerve, cerebellum, and cerebrum. Deficits can include weakness, loss of coordination, visual loss, cognitive impairment, and loss of bowel and/or bladder control, among others. These system-based symptoms are generally superimposed on more chronic, pervasive symptoms, including mood disorder, neuropathic pain, fatigue, and sexual dysfunction.

1.1.2 Ocrelizumab

OCR binds to human CD20 with high affinity, selectively depleting B cells through several mechanisms, including antibody-dependent cell–mediated phagocytosis, antibody–dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.

OCR is also known as Ro 4964913, PRO70769, and rhuMAb 2H7 (refer to the Ocrelizumab Investigator's Brochure for further information).

1.1.3 Sponsor Experience with Anti-CD20 Compounds in Multiple Sclerosis

The ongoing clinical development program to investigate the safety and efficacy of OCR in patients with both relapsing forms (i.e., RMS and relapsing-remitting MS [RRMS]) and primary progressive MS (PPMS) includes an ongoing open-label extension (OLE) of the Phase II Study WA21493/ACT4422G for RRMS patients and three ongoing Phase III pivotal trials: 2 in RMS (WA21092 and WA21093) and 1 in PPMS (WA25046).

1.1.3.1 Ocrelizumab in Relapsing Forms of Multiple Sclerosis (RMS)

Study WA21493 (which started in January 2008) is a Phase II, randomized, multicenter, placebo-controlled, double-blind, dose-finding study to evaluate the efficacy and safety of OCR in patients with RRMS. The controlled treatment period of Study WA21493 was completed at Week 24, and the open-label period of the study is ongoing. Data from the 96-week treatment period and the 48-week treatment-free period (Week 144 data) are presented in the Ocrelizumab Investigator's Brochure.

Data presented below are from the completed double-blind, double-dummy treatment period of the two pivotal Phase III studies in RMS (Studies WA21092 and WA21093) up to the clinical cutoff dates of 2 April 2015 and 12 May 2015, respectively. The efficacy results as well as the pooled analysis from these pivotal studies show that OCR suppresses relapses and disease progression (clinical and subclinical disease activity) compared with interferon (IFN) β-1a 44 μg SC in patients with RMS over the course of 2 years (96 weeks).

Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints.

In comparison with IFN β-1a 44 μg SC, OCR 600 mg demonstrated:

- Relative reductions of 46% and 47% for the primary endpoint of protocol-defined annualized relapse rate in Studies WA21092 and in WA21093, respectively (both $p < 0.0001$)
- A 40% risk reduction for 12-week confirmed disability progression (CDP) in the pooled Study WA21092/WA21093 analysis ($p = 0.0006$). Each individual trial also demonstrated a significant reduction of 12-week CDP (43% reduction [$p = 0.0139$] in Study WA21092 and 37% [$p = 0.0169$] in Study WA21093).
- Relative reductions of 94% and 95% in the number of T1 gadolinium (Gd)-enhancing lesions in Studies WA21092 and WA21093, respectively (both $p < 0.0001$)
- Relative reductions of 77% and 83% in the total number of new and/or enlarging T2 lesions in Studies WA21092 and WA21093, respectively (both $p < 0.0001$)
- A 33% relative increase in proportion of patients with 12-week confirmed disability improvement (CDI) in the pooled Study WA21092/WA21093 analysis ($p = 0.0194$). Study WA20192 demonstrated a 61% relative increase in the proportion of patients with 12-week CDI ($p = 0.0106$), whereas in Study WA21093, there was no statistically significant difference between treatment groups (14% relative increase, $p = 0.4019$).
- A 40% risk reduction for 24-week CDP in the pooled Study WA21092/WA21093 analysis ($p = 0.0025$). Each individual trial also demonstrated a significant reduction of 24-week CDP (43% reduction [$p = 0.0278$] in Study WA21092 and 37% [$p = 0.0370$] in Study WA21093).

- Relative reductions of 57% and 64% (both $p < 0.0001$) in the total number of new T1 hypointense lesions (chronic black holes) in Studies WA21092 and WA21093, respectively

OCR also showed numerically superior outcomes in additional secondary efficacy endpoints in the following hierarchical order (for results where the formal testing procedure had previously concluded, p-values are indicated as "non-confirmatory"):

- Greater mean improvement in the Multiple Sclerosis Functional Composite Scale from baseline to Week 96 in Study WA21092 ($p = 0.3261$) and Study WA21093 ($p = 0.0040$)
- Relative reduction in rate of brain volume loss from Week 24 to Week 96 of 22.8% in Study WA21092 (non-confirmatory, $p = 0.0042$) and 14.9% in Study WA21093 ($p = 0.0900$)
- Higher mean change in SF-36 Physical Component Summary score from baseline to Week 96 in Study WA21092 (non-confirmatory, $p = 0.2193$) and Study WA21093 (non-confirmatory, $p = 0.0404$)
- 74% and 81% relative increases in the proportion of patients with no evidence of disease activity in Studies WA21092 and WA21093, respectively (non-confirmatory, $p < 0.0001$ for both studies in patients with Expanded Disability Status Scale [EDSS] ≥ 2)

Robust data from the two pivotal Phase III studies WA21092 and WA21093 presented above provide compelling evidence of the efficacy of OCR in patients with RMS.

1.1.3.2 Safety in Multiple Sclerosis

Safety data presented below are from the completed controlled treatment periods of the two pivotal Phase III studies in RMS (WA21092 and WA21093) and the Phase III study in PPMS (WA25046). For more information on data from controlled treatment periods and OLE periods from ongoing studies, refer to the Ocrelizumab Investigator's Brochure. In the 96-week controlled treatment period of the Phase III RMS studies (WA21092 and WA21093), a total of 1651 patients received study drug and were included in the safety analyses of the pooled data (IFN β-1a: 826 patients; OCR: 825 patients).

The safety profile in the IFN β-1a treatment group was consistent with the labeled safety information available for IFN β-1a. Compared with results from the Phase II study in RRMS (WA21493), there were no new or unexpected safety findings associated with OCR during the 96-week controlled treatment period.

The number of patients who experienced any adverse event (83.3% in both groups) and the total number of adverse events (IFN β-1a: 4141 adverse events; OCR: 4194 adverse events) were well balanced between the two treatment groups; the majority of adverse events were Grade 1 or Grade 2. The proportion of patients who experienced a serious adverse event (IFN β-1a: 8.7% vs. OCR: 6.9%) was similar between treatment

groups. Overall, the rates of adverse events, including serious, remained stable with additional exposure to OCR.

A total of 725 patients in the Phase III PPMS controlled treatment period received study drug and were included in the safety analysis (placebo: 239 patients; OCR: 486 patients). The proportion of patients who experienced at least one adverse event was 90% in the placebo treatment group compared with 95.1% in the OCR treatment group; the majority of adverse events were Grade 1 or 2. The proportion of patients who experienced a serious adverse event (placebo: 22.2% vs. OCR: 20.4%) was similar in both groups. The intensity of most serious adverse events was reported as Grade 3.

Further details are provided in the periodically updated Ocrelizumab Investigator's Brochure.

To date, there are no known major safety concerns but known risks for patients being treated with OCR; these are discussed in Section 5.1. Also refer to the latest Ocrelizumab Investigator's Brochure.

1.1.4 Vaccine Response with Ocrelizumab

OCR significantly and rapidly reduces the number of peripheral CD20+B cells. In the Phase II study WA21493, all patients had completely depleted CD19+ cells by Day 15 (99% mean and median change from baseline) and by Week 24, no patient had demonstrated any return of peripheral CD19+ cell counts to baseline values or to the lower limit of normal (LLN) of 80 cells/μL, (i.e., the protocol-defined measure of recovery). B cells repleted for >50% of the patients in all treatment groups by Week 144, except for in the OCR 1000 mg group (where 56.4% of the patients were still depleted at Week 144). The relevance of patients not having repleted B-cell levels (i.e., returned to LLN or baseline) to their response to vaccination is not known.

Results from the Immunization Study Period of this study BN29739 indicate that patients being treated with OCR may have an attenuated humoral response when immunized with an inactivated vaccine. The detailed BN29739 study results can be found in the current version of the Ocrelizumab Investigator's Brochure.

An integrated analysis of MS patients treated with OCR treatment revealed that after treatment with OCR over 2 years, the proportion of patients with positive antibody titers against Streptococcus pneumoniae, mumps, rubella, and varicella was generally similar to the proportions at baseline.

1.2 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study (BN29739) is being performed to characterize humoral immunity to a variety of antigens by evaluating immunization responses in patients with RMS who are treated with OCR.

This study plans to use the following vaccines to evaluate different immune response pathways after administration of a course of OCR in patients with RMS:

- The TT-containing vaccination was chosen to assess the T-cell dependent anamnestic humoral response.
- The 23-valent PPV (23-PPV) vaccination was chosen to assess a mostly T-cell independent or pure 'B-cell' humoral response.
- KLH was chosen to explore immune response to neo-antigen.
- The influenza vaccination was chosen as it is considered important from a clinical perspective.
- The booster 13-valent conjugate pneumococcal vaccine (13-PCV) was chosen to assess the clinical efficacy of the 23-PPV vaccine followed by the booster 13-PCV compared to 23-PPV vaccine alone.

Characterization of the humoral immune response in RMS patients who have received OCR will provide guidance regarding the efficacy and safety of vaccine administration in these patients. Please refer to Section 3.1 for further details on study design.

Substantial measures have been taken to enroll only appropriate patients and to decrease the risk to patients who participate in this study. Refer to eligibility criteria in Section 4.1 and the safety plan in Section 5.1, respectively.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

- To characterize the humoral immune response (IgG) to TT vaccine in patients with RMS who are treated with OCR (Group A), compared with that of patients with RMS who are not treated with OCR (Group B).

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

1. To characterize the humoral immune response (IgG) to the 23-PPV in Group A (Groups A1 and A2) patients compared with Group B patients.
2. To characterize the humoral immune response (IgG) in OCR-treated patients to 23-PPV boosted by a subsequent 13-PCV booster (Group A1) compared with unboosted 23-PPV (Group A2).
3. To characterize the humoral immune response (IgG and IgM) to KLH in Group A patients compared with Group B patients.
4. To characterize the humoral immune response (HI titers) to influenza vaccine in OCR-treated patients (Group A2) patients compared with patients not treated with OCR (Group B).

5. To evaluate the long-term effects of OCR on MRI parameters of disease activity during the Optional Ocrelizumab Extension (OOE) Period of the study.

Group A will be split into Group A1 (patients will receive the booster 13-PCV), and Group A2 (patients will receive the influenza vaccine; see Section 3.1).

2.3 SAFETY OBJECTIVES

The safety objectives for this study are to collect additional data on the safety of OCR.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This Phase IIIb, multicenter, randomized, open-label study is designed to evaluate immune response to vaccines after administration of a dose of OCR (i.e., a dual infusion of OCR 300 mg on Day 1/Week 1 [Dose 1 Infusion 1] and Day 15/Week 2 [Dose 1 Infusion 2]) in patients with RMS.

Following screening, approximately 100 adult patients will be randomized into Groups A and B (2:1; active:control) to compare responses to immunization. Patients in Group B are to receive immunization with TT-containing adsorbed vaccine, 23-PPV, influenza vaccine, and repeated administration with KLH. Group B patients will not receive OCR but will remain on no MS-specific disease-modifying therapy (DMT) or continue with IFN-β treatment until optional OCR treatment at the end of the Immunization Study Period.

Patients in Group A are to first receive OCR (Day 1/Week 1 [Dose 1 Infusion 1] and Day 15/Week 2 [Dose 1 Infusion 2]), and 12 weeks post-OCR treatment, are to receive a similar immunization course to Group B. Group A will be further subdivided into two groups to evaluate the effectiveness of a booster 13-PCV vaccination or of influenza vaccination.

For the primary objective and for secondary objectives 1 and 3 (see Sections 2.1 and 2.2, respectively), Group A (active) will be compared with Group B (control).

To determine the outcomes of secondary objectives 2 and 4, patients in Group A will be split into two groups with 50% of patients in each group (Groups A1 and A2). Patients will be assigned to either Group A1 or A2:

- Group A1 will receive booster 13-PCV (approximately 33 patients)
- Group A2 will receive the influenza vaccine (approximately 33 patients but a minimum of 30 patients).

A minimum of 30 patients will be assigned to Group A2 during the first influenza season. If a minimum of 30 patients (a maximum of 33) are assigned to Group A2 and receive the first year's influenza vaccine, all remaining patients in Group A will be assigned to

Group A1 and receive the 13-PCV booster. If less than 30 patients have been assigned to Group A2 during the first influenza season, further patients assigned to Group A2 will have influenza vaccine visits during the subsequent influenza season (i.e., when the next year's vaccine becomes available).

The primary and secondary humoral immunity and immunophenotyping outcomes are to be measured by flow cytometry and quantitative Ig measurements.

Approximately 30–35 centers will participate in the study in the United States/ North America. This study consists of up to five study periods:

- Screening Period
- Immunization Study Period

  Group A: Immunization Study Period and OCR treatment starts at Day 1/Week 1. Patients will receive 300 mg of open-label OCR on Day/Week 1 (Dose 1 Infusion 1) and Day 15/Week 2 (Dose 1 Infusion 2). Patients in Group A will be split and be assigned to either Group A1 (booster 13-PCV) or Group A2 (influenza vaccine). At Day 85/Week 12 patients will start to receive immunizations and undergo post-immunization assessments. For all patients in Group A, the Immunization Study Period will end on Day 169/Week 24.

  Group B: Patients will not receive OCR. At Day 1/Week 1, patients will start to receive immunizations and undergo post-immunization assessments. For Group B, the Immunization Study Period will end at Day 84/Week 12.

  The timing of immunizations and post-baseline assessments are detailed in Appendix 1.

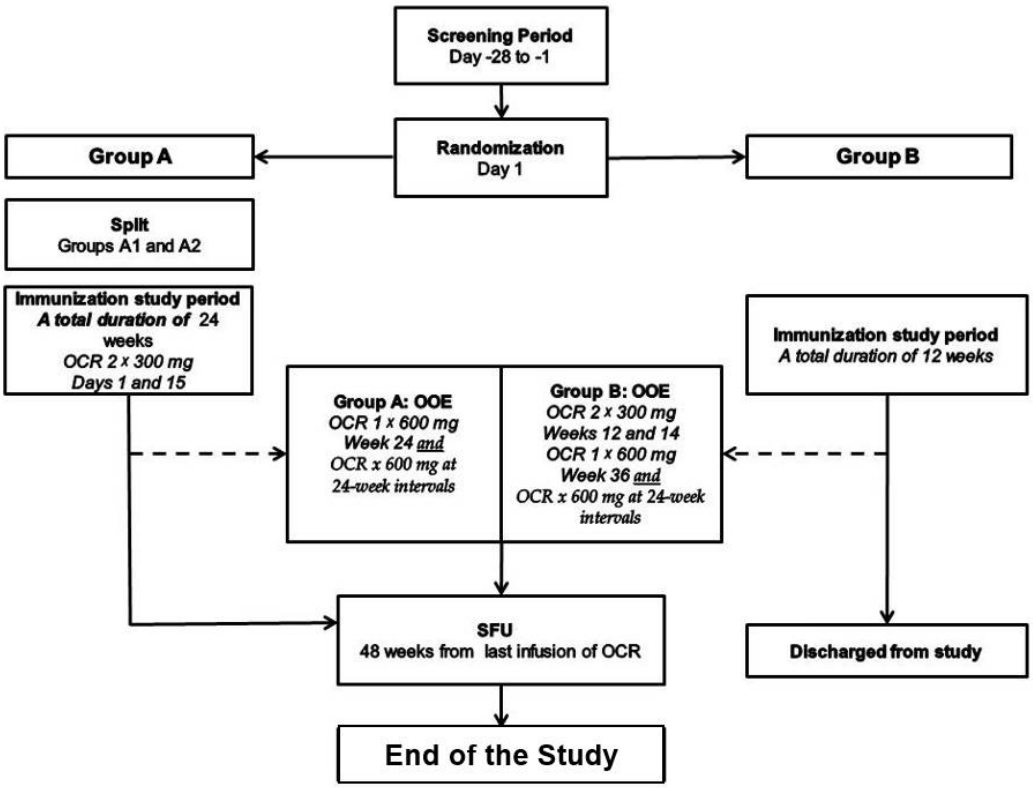
- Optional OCR Extension (OOE) Period:
  - **Groups A1 and A2**: Patients who complete the 24–week immunization study period will have the option for retreatment with a single infusion of 600 mg OCR (Dose 2) at Day 169/Week 24 and subsequent single infusions (600 mg OCR) at intervals of 24 weeks provided that he or she meets the OOE retreatment criteria and chooses to receive retreatment.
  - **Group B**: Patients who complete the 12–week immunization study period will have the option to receive OCR in the OOE; the first dose will be administered as two single infusions of 300 mg, on Day 84/Week 12 (Dose 1 Infusion 1) and Day 98/Week 14 (Dose 1 Infusion 2), and subsequent doses will be administered as single 600 mg infusions (Dose 2, Dose 3, etc.) at intervals of 24 weeks provided that he or she meets the OOE retreatment criteria and chooses to receive retreatment. Group B patients who do not qualify for and/or do not choose treatment with OCR at Week 12 will complete the study at Week 12 and will **not** enter safety follow-up.

Please note that the OOE will continue with all patients who are able to receive OCR as per local guidelines, or unless the Sponsor decides to terminate the OCR program for MS; however, the OOE will not exceed 4 years after the last patient last visit in the Immunization Study Period. *At the end of the OOE, patients may choose to continue on commercially available OCR.*

- Safety Follow-Up (SFU) Period: *Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start treatment with commercial OCR, they will be discontinued from the SFU and from the study.*

A schedule of assessments is provided in Appendix 1. Study Schemas are provided in Figure 1 and Figure 2.

Figure 1 Schema of Study Periods



OCR = ocrelizumab; OOE = Optional Ocrelizumab Extension Period; SFU = safety follow-up.

Figure 2 Study Schema

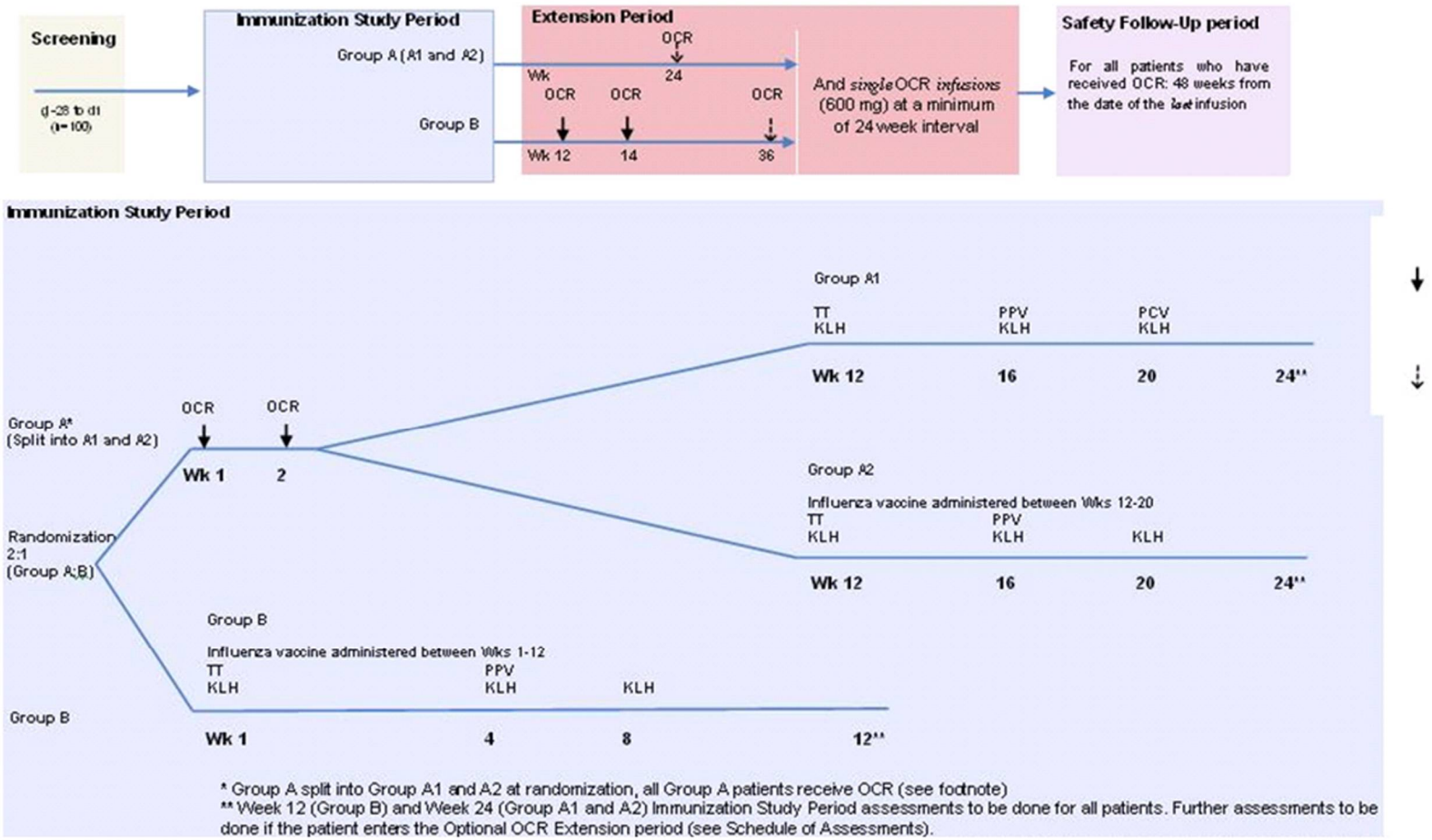


Figure 2 Study Schema (cont.)

KLH = keyhole limpet heamocyanin; $OCR = ocrelizumab;$ PCV = pneumococcal conjugate vaccine; PPV = polysaccharide pneumococcal vaccine; TT = tetanus toxoid-containing vaccine; Wk = week

Influenza vaccine: Group B: The influenza vaccine can be given any time between Week 1 and 12. If a patient needs to receive the vaccine after Week 12, the OCR infusion can be delayed. For patients in Group A2 and Group B who, as per the Schedule of Assessment, are due to receive the influenza vaccine during their country-specific influenza vaccine blackout period, administration of the vaccine should be given prior to the start of this blackout period.

***Group A split:** Patients assigned to Group A2 will receive the influenza vaccine. Patients assigned to Group A1 will receive the 13-PCV booster.

3.2 END OF STUDY

The end of study is defined as the last patient last visit in the Safety Follow-Up Period.

3.3 RATIONALE FOR STUDY DESIGN

The primary objective of this study is to characterize the effects of OCR on immune responses in patients with RMS as measured by vaccine titers. The randomized, open-label nature of this study is not expected to significantly affect vaccine titers in either Group A or B (active or control, respectively).

3.3.1 Rationale for Specific Antigens

This trial will investigate the effect of B-cell depletion by OCR on primary humoral response, recall response, and persistent acquired immunity to specific antigens.

- A TT-containing adsorbed vaccine will be administered to assess whether one dose of OCR affects the integrity of a T-cell–dependent anamnestic humoral response.
- A 23-valent PPV has been selected to assess a mostly T-cell independent or 'pure B-cell' humoral response for a clinically relevant antigen.
- KLH will be used to test primary humoral neoantigen response as it is a novel immunogen for most individuals.
- An influenza vaccine has been selected to test the ability to mount a humoral immune response to a clinically relevant vaccine.

3.3.2 Rationale for Timing of Vaccinations

Experience with OCR in MS in the Phase II study (Study WA21493/ACT4422G) has determined that the majority of patients are still peripherally CD19–positive B-cell depleted between 12 and 24 weeks post-treatment. Therefore, Day 85/Week 12 is an appropriate time to begin vaccinations in patients to evaluate the effect of peripheral CD19–positive B-cell depletion by OCR on immune response to vaccination.

3.3.2.1 Tetanus Toxoid Adsorbed Vaccine

TT vaccine will be administered as a combined adsorbed vaccine with diphtheria (tetanus-diphtheria [Td] or diphtheria and tetanus toxoid [DT]) or with diphtheria and acellular pertussis (diptheria-tetanus-acellular pertussis [DTaP] or tetanus-diphtheria-acellular pertussis [Tdap]).

Group A (active) patients will receive a TT-containing vaccine 12 weeks after the first OCR administration. Serum anti-tetanus titers will be measured 4 and 8 weeks after vaccine administration and compared with levels immediately prior to vaccine administration.

Group B (control) patients will not receive OCR during the Immunization Study Period. They will receive a TT-containing vaccine at Day 1/Week 1. Serum anti-tetanus titers will be measured 4 and 8 weeks after vaccine administration (Day 28/Week 4 and

Day 56/Week 8) and will be compared with levels immediately prior to vaccine administration.

3.3.2.2 23-Valent Pneumococcal Polysaccharide Vaccine

The 23-PPV will be administered to Group A (active) patients 16 weeks after the first OCR administration. Serum titers against all 23 serotypes (1, 2, 3, 4, 5, 6b, 7F, 8,9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F) will be measured 4 and 8 weeks after vaccine administration and will be compared with levels immediately prior to vaccine administration.

Group B patients will receive the 23-PPV vaccine at Day 28/Week 4. Serum titers will be measured 4 and 8 weeks after vaccine administration and will be compared with levels immediately prior to vaccine administration.

3.3.2.3 Keyhole Limpet Hemocyanin

Group A (active) patients will receive KLH at 12, 16, and 20 weeks after OCR administration. Serum titers will be measured 4, 8, and 12 weeks after the initial KLH administration (Day 112/Week 16, Day 140/Week 20, and Day 169/Week 24) and will be compared with levels immediately prior to the first KLH administration.

Group B patients will receive KLH at Day 1/Week 1, Day 28/Week 4, and Day 56/Week 8. Serum titers will be measured 4 weeks after KLH administration (Day 28/Week 4, Day 56/Week 8, and Day 84/Week 12) and will be compared with levels immediately prior to the first KLH administration.

3.3.2.4 Influenza Vaccine

Group A (active) patients are to be split and patients assigned to Group A2 will receive the influenza vaccine after OCR administration (refer to Section 3.1 for details on the assignment on patients to Group A1 or A2). Patients can receive the influenza vaccine at any time between Weeks 12 and 20. Serum titers will be measured 4 weeks after the initial vaccine administration and will be compared with levels immediately prior to vaccine administration.

Group B patients can receive the influenza vaccine between Week 1 and 12. If necessary, Group B patients can receive the influenza vaccine after Week 12, in which case the OCR infusion visit must be delayed. Serum titers will be measured 4 weeks after vaccine administration and will be compared with levels immediately prior to vaccine administration.

Group A1 patients can receive the influenza vaccine at any time at the discretion of the investigator.

3.3.2.5 Conjugate Pneumococcal Vaccine Booster (13-PCV)

Group A (active) patients will be split at randomization and approximately 33 patients will be in Group A1 and receive a booster 13-PCV at Day 140/Week 20 (refer to Section 3.1

for details on the assignment on patients to Group A1 or A2). Serum antibody titers will be measured 4 weeks after the booster 13-PCV administration (Day 169/Week 24).

3.3.3 Rationale for Ocrelizumab Dose Selection

The dose of 600 mg of OCR administered intravenously (IV; given as dual infusions of 300 mg on Days 1 (Dose 1 Infusion 1) and 15 (Dose 1 Infusion 2) for the first dose and subsequently as a single infusion of 600 mg every 24 weeks) is under investigation in the Phase III RMS clinical program. This has been selected as a clinically appropriate dose based on the results from Study WA21493/ACT4422g.

3.3.4 Rationale for Group B

In Group B, patients will be eligible for the study provided that they are on no MS-specific DMT or continuing with IFN-β treatment.

Group B patients will enter the study on their current IFN-β MS treatment or remain on no MS-specific DMT until Week 12 at which point they can receive OCR (300 mg $\times$ 2 infusions at Day 84/Week 12 and Day 98/Week 14). The study has been designed with the shortest Immunization Study Period feasible for patients in Group B before they can receive OCR.

3.3.5 Rationale for the Safety Follow-Up Period

Data collected during this period *will allow evaluation of safety after OCR treatment is stopped.*

3.4 OUTCOME MEASURES

3.4.1 Primary Immunization Outcome Measure

The primary outcome measure is the proportion of patients in Groups A (i.e., combined Groups A1 and A2) and B with a positive response (IgG) to TT vaccine measured 8 weeks after TT vaccine administration.

For patients with pre-immunization tetanus antibody titers $<$ 0.1 IU/mL, a positive response to the booster immunization is defined as an antibody titer $\geq$ 0.2 IU/mL measured 8 weeks after immunization. For patients with pre-immunization tetanus antibody titers $\geq$ 0.1 IU/mL, positive response to the booster immunization is defined as a 4-fold increase in antibody titers compared with pre-vaccination levels measured 8 weeks after immunization. Pre-immunization levels are those obtained immediately prior to administration of a vaccine.

3.4.2 Secondary Outcome Measures

The secondary outcome measures are as follows:

- TT response:
  - The proportion of patients in Groups A (A1 and A2) and B with a positive response (IgG) to TT vaccine measured 4 weeks after TT vaccine administration.
  - The proportion of patients in Groups A (A1 and A2) and B with a 2-fold increase in tetanus antibody titers, or with tetanus antibody titers $\geq$ 0.2 IU/mL, measured 4 weeks after the immunization of patients with pre-immunization tetanus antibody titers $\geq$ 0.1 IU/mL or with pre-immunization tetanus antibody titers $<$ 0.1 IU/mL, respectively.
  - Mean levels of anti-tetanus antibody in patients in Groups A (A1 and A2) and B measured immediately prior to and 4 weeks after a booster TT vaccine.
- Pneumococcal vaccine response:
  - The proportion of patients in Groups A (A1 and A2) and B with positive antibody responses against an individual pneumococcal serotype measured 4 weeks after the 23-PPV (23 serotypes). (A positive response against a serotype is defined as developing a 2-fold increase in antibody level or a $>$ 1 μg/mL rise in level compared with pre-immunization levels. Pre-immunization levels are those obtained immediately prior to receipt of 23-PPV.) Post-immunization levels will be measured 4 and 8 weeks after 23-PPV administration for Groups A1, A2, and B.
  - The proportion of patients in Groups A (A1 and A2) and B with a positive response against at least 2 out of 23 pneumococcal antibody serotypes measured 4 weeks after administration of 23-PPV vaccine.
  - The proportion of patients in Groups A (A1 and A2) and B with positive responses against at least 50% of the serotypes ($\geq$ 12 of 23) measured 4 weeks after administration of 23-PPV vaccine.
  - Mean levels of anti-pneumococcal serotype-specific antibody in patients in Groups A (A1 and A2) and B measured immediately prior to and 4 and 8 weeks (which is 4 weeks after Group A1 patients received the 13-PCV booster) after administration of 23-PPV vaccine.
- KLH response:
  - Mean levels of anti-KLH antibody (IgG and IgM) in patients in Groups A (A1 and A2) and B measured immediately prior to the first administration of KLH and 4 weeks after the last administration of KLH.
  - Mean levels of anti KLH antibodies (IgG and IgM) in patients in Groups A (A1 and A2) and B measured over time at 4, 8, and 12 weeks after first KLH administration.

- Strain-specific influenza vaccine response in Groups A2 and B:
  - Proportion of patients who achieve seroprotection defined as specific HI titers >40 at 4 weeks post-immunization
  - Proportion of patients who achieve a 2-fold increase in specific HI titers at 4 weeks post-immunization
  - Proportion of patients who achieve a 4-fold increase in specific HI titers at 4 weeks post-immunization
  - Proportion of patients with seroconversion (i.e., a pre-vaccination antibody titer <10 and a post-vaccination HI titer >40);
  - Strain–specific geometric mean titers (GMTs) at baseline and at 4 weeks post-vaccination
  - Strain–specific GMT ratio (post-vaccination:pre-vaccination)
- MRI assessments to evaluate the long-term effects of OCR on MRI parameters of disease activity during the OOE Period.

3.4.3 Immunophenotyping Outcome Measures

The humoral and cellular immunity outcome measures in this study are as follows:

- Flow cytometry, which will include (but is not limited to) the following cells:
  - Total B cells (CD19 positive)
  - B-cell subsets, e.g., memory B cells, naïve B cells, plasma cells
  - Total T cells (CD3 positive)
  - T helper cells (CD3 positive, CD4 positive)
  - Cytotoxic T lymphocytes (TCTL; CD3 positive, CD8 positive)
  - NK cells (CD3 negative, CD16/56 positive)
- Quantitative Ig: Ig levels (including total Ig, IgG, IgG subtypes, IgM, and IgA)

3.4.4 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Vital signs*, hematologic laboratory tests, anti-drug antibody (ADA) formation, physical and neurological examinations, and the incidence and severity of adverse events associated with OCR and study immunizations.

**To monitor infusion-related reactions (IRRs), vital signs will be obtained immediately pre-infusion, every 15 ($\pm$5) minutes for the first hour during the infusion, every 30 ($\pm$5) minutes for the remainder of the infusion, and at the end of the infusion on days of OCR administration.*

4. MATERIALS AND METHODS

4.1 PATIENTS

Adult patients with RMS who fulfill the eligibility criteria specified in Sections 4.1.1 and 4.1.2 are eligible for enrollment into the study. For the eligibility criteria for the OOE period, see Section 4.1.3 and Section 4.1.4.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent and to be able to follow the protocol–defined schedule of assessments
- Diagnosis of RMS in accordance with the revised McDonald criteria (Polman et al. 2011)
- Age 18–55 years, inclusive
- Received at least one previous immunization against TT or tetanus and diphtheria (DT/Td) or tetanus, diphtheria, and acellular pertussis (DTaP/Tdap).
- Expanded Disability Status Scale (EDSS) at screening from 0–5.5 points, inclusive
- Contraception requirements:
  - **For sexually active female patients of reproductive potential**, use of reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, is required):*
    - One primary method of contraception throughout the trial, including the active treatment phase AND for 6 months after the last dose of OCR.

    **Acceptable methods of contraception include one primary (e.g., systemic hormonal contraception or tubal ligation, vasectomy of the male partner) OR a double-barrier method (e.g., latex condom, intrauterine device, vaginal ring or pessary plus spermicide [e.g., foam, vaginal suppository, gel, cream]).*

  - For female patients without reproductive potential:
    - Women may be enrolled if post-menopausal (i.e., spontaneous amenorrhea for 12 months confirmed by a follicle stimulating hormone [FSH] level >40 mIU/mL) unless the patient is receiving a hormonal therapy for her menopause; or surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

4.1.2 Exclusion Criteria

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

- Contraindications for or intolerance to oral or IV corticosteroids, including methylprednisolone administered IV, according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents
- Known presence of other neurologic disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T–lymphotropic virus-1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders that potentially cause progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren'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 PML
- Patients who meet the following criteria related to their general health will be excluded:
  - Pregnancy or lactation
  - Lack of peripheral venous access
  - History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
  - Known hypersensitivity to any component of the TT-containing adsorbed vaccine, including thiomersal (thimerosal in United States)
  - History of systematic allergic, neurologic, or other reactions following a previous dose of any TT-containing vaccine

  - Known hypersensitivity to any component of any pneumococcal polysaccharide or conjugate vaccine
  - Known hypersensitivity to any component of the influenza vaccine
  - Allergy to shellfish
  - Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, or gastrointestinal or any other significant disease that may preclude a patient from participating in the study
  - Congestive heart failure (New York Heart Association III or 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 major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit or oral antibiotics within 2 weeks prior to baseline visit
  - History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)
  - History of recurrent aspiration pneumonia that required antibiotic therapy
  - History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix of the uterus that have been excised and resolved, with documented clean margins on pathology)
  - Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
  - History of alcohol or drug abuse within 24 weeks prior to randomization
  - History of or currently active primary or secondary immunodeficiency
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or 5 half-lives of the investigational drug, whichever is longer, or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Receipt of any pneumococcal vaccine within 5 years prior to screening
- Previous exposure to KLH
- Previous immunization with any tetanus-containing vaccine within 2 years prior to screening
- If scheduled as per protocol to receive the 2015/2016 vaccine and has already received the 2015/2016 vaccine or if scheduled as per protocol to receive the 2016/2017 vaccine and has already received the 2016/2017 vaccine.

- Receipt of a live vaccine within 6 weeks prior to randomization*

  **Vaccinations before baseline: in rare cases where a live vaccine must be administered by the patient's physician, the screening period may need to be prolonged but cannot exceed 8 weeks.*

- Previous treatment with B-cell targeted therapies (e.g., RTX, OCR, atacicept, belimumab, or ofatumumab)
- Any previous treatment with alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, MTX, total body irradiation, or bone marrow transplantation
- Any previous treatment with lymphocyte-trafficking blockers (e.g., natalizumab, fingolimod)
- Treatment with IV Ig, plasmapheresis, teriflunomide or dimethyl fumarate, or glatiramer acetate within 12 weeks prior to randomization*
- Systemic corticosteroid therapy within 4 weeks prior to screening**

  ** Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility criteria for the trial. Patients who discontinue their current therapy for non-medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may not receive RMS disease–modifying therapies. Group B patients can continue with IFN-β treatment. If the patient has received teriflunomide he or she may need to go through the accelerated elimination protocol (Genzyme 2013).*

  ***The screening period may be extended (but cannot exceed 8 weeks) for patients who have used systemic corticosteroids for RMS before screening. In addition, for a patient to be eligible, systemic corticosteroids should not have been administered between screening and baseline.*

- Exclusions related to laboratory findings:*
  - Positive serum β-human chorionic gonadotropin (hCG) measured at screening
  - 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)
  - Positive rapid plasma reagin (RPR), if confirmed by microhemagglutination assay or fluorescent treponemal antibody absorption test
  - CD4 count $< 300/\mu L$
  - Serum creatinine > 1.4 mg/dL (> 124 μmol/L) for women or > 1.6 mg/dL (> 141 μmol/L) for men
  - AST/SGOT or ALT/SGPT $\geq 2.0 \times$ upper limit of normal (ULN)
  - Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9$/L)
  - Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)

- ANC $< 1.5 \times 10^3/\mu L$
- Levels of serum IgG 18% below the LLN (for central laboratory: IgG < 4.6 g/L)
- Levels of serum IgM 8% below the LLN (for central laboratory: IgM < 0.37 g/L)

** Retesting before baseline: in rare cases in which the screening laboratory samples are rejected by the central laboratory (example: hemolyzed sample) or the result is not assessable (example: indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria. In such circumstances, the screening period may need to be prolonged but cannot exceed 8 weeks.*

Based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude TB (e.g., chest X-ray, tuberculin skin or blood test), Lyme disease, HTLV-1–associated myelopathy (HAM), AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the investigator.

4.1.3 Eligibility for the Optional Ocrelizumab Extension Period

Only patients who have completed the Immunization Study Period are potentially eligible for the Optional OCR Extension Period.

Prior to re-treatment with OCR, patients will be evaluated for the following conditions and laboratory abnormalities.

4.1.4 Re-treatment Criteria

Prior to re-treatment, the following conditions must be met:

- Absence of severe allergic or anaphylactic reaction to a previous OCR infusion
- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Absence of active infection (including active TB infection, either new onset or reactivation)*
- ANC $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test**

If any of the conditions are not met prior to re-treatment, further administration of OCR should be suspended until resolved or held indefinitely.

* Patients with active TB infection, either new onset or reactivation, must suspend ocrelizumab treatment for as long as needed to ensure full resolution of the TB

infection. These patients should receive medical care in adherence with local/national requirements until complete resolution of the TB infection and should be monitored subsequently as per local medical plans. Upon resolution of the TB infection and based on individual benefit-risk assessments, these patients will have the opportunity to re-start ocrelizumab treatment if it is considered beneficial for them. Otherwise, the treating Investigator can decide to permanently stop ocrelizumab.

*** In the event of pregnancy, the Investigator must counsel the patient as to the risks of continuing with the pregnancy and the possible effects on the fetus. Given there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the completion of pregnancy and breastfeeding. Pregnant and breastfeeding patients should continue to follow the schedule of assessments for the OOE; however, no infusions will occur. If there is a concern with the ability of a pregnant or breastfeeding patient to perform all scheduled assessments, the Investigator must contact the Medical Monitor for further discussion. In the OOE period of the study, re-start of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit/risk discussion between the patient and investigator.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Subjects will be randomized in a 2:1 ratio to Group A (OCR) or Group B. Randomization will be performed by an independent vendor via an interactive response system (IxRS).

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study drug will be in accordance with Roche standards and local regulations.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

Ocrelizumab Formulation

OCR is a clear or slightly opalescent, colorless to pale brown solution supplied as a liquid formulation containing 30 mg/mL OCR in 20 mM sodium acetate at pH 5.3, with 4% (106 mM) trehalose dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15 cc Type I USP glass vial, fitted with a

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

Ocrelizumab Packaging

The hospital units/pharmacy will receive study medication kits for each patient. Each study medication kit will contain one single-use liquid vial OCR.

For Dose 1, consisting of two 300 mg infusions 14 days apart, one study medication kit will be used per visit.

For subsequent doses, a 600 mg OCR infusion in the OOE, two study medication kits will be used per visit.

Ocrelizumab Preparation

OCR drug product must be diluted before administration. Solutions of OCR 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 1–2 mg/mL.

Detailed instructions are provided in the Dose Preparation Guidelines.

Storage of Ocrelizumab Vials for Infusion

OCR vials are stable at 2°C–8°C (refrigerated storage). They should not be used beyond the expiration date. Expiration dating may be extended during the trial; the Sponsor will provide documentation. OCR vials should not be frozen or shaken and should be protected from direct sunlight. The study drug labels will be produced in accordance with the local requirements.

The prepared infusion solution of OCR is physically and chemically stable for 24 hours at 2°C–8°C and subsequently for 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored for up to 24 hours at 2°C–8°C. Infusion solution must be completely administered to the patient within 32 hours of preparation (not to exceed 24 hours at 2°C–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.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low–protein-binding filter (pore size of 0.2 to 0.22 μm). OCR may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if it is discolored or if the solution contains discrete foreign particulate matter.

Mandatory premedication is required prior to any infusion with OCR (see Section 4.4.1).

During the Immunization Study Period:

- Patients in Group A will be administered OCR by IV infusion at a dose of 300 mg on Day 1/Week 1 (Dose 1 Infusion 1) and Day 15/Week 2 (Dose 1 Infusion 2).
- Patients in Group B will not receive any OCR.

During the OOE, for patients who meet the criteria for optional OCR treatment (refer to Section 4.1.3 and Section 4.1.4):

- Patients from Groups A1 and A2 will be administered OCR by IV infusion at a dose of 600 mg on Day 169/Week 24 (Dose 2) and subsequent 600 mg single infusions with an interval of 24 weeks (minimum interval of 22 weeks).
- Patients from Group B will be administered OCR by IV infusion at a dose of 300 mg on Day 84/Week 12 (Dose 1 Infusion 1) and Day 98/Week 14 (Dose 1 Infusion 2) and at a dose of 600 mg on Day 252/Week 36 (Dose 2) and subsequent 600 mg single infusions with an interval of 24 weeks (minimum interval of 22 weeks).

4.4 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

4.4.1 Premedication

Premedication is mandatory with methylprednisolone 100 mg IV 30 minutes prior to each infusion of OCR, and with an antihistaminic drug (e.g., diphenhydramine) approximately 30–60 minutes prior to each infusion of OCR. In the rare case when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative steroid should be used as premedication prior to the infusion.

Pre-infusion treatment with an oral analgesic/antipyretic (e.g., acetaminophen) 30–60 minutes prior to each infusion of OCR is also recommended.

4.4.2 Immunizations

4.4.2.1 Tetanus Toxoid Vaccine

TT vaccine is indicated for the prevention of tetanus. The TT vaccine will be administered as part of the combined adsorbed vaccine with diphtheria (Td/DT) and/or acellular pertussis (DTaP/Tdap). In this study, TT adsorbed vaccine is being used to assess whether OCR affects antibody production to an antigen to which individuals have pre-existing immunity.

Group A patients will receive a TT-containing adsorbed vaccine (0.5 mL) as an intramuscular (IM) injection in the deltoid muscle at Day 85/Week 12.

Group B patients will receive a TT-containing adsorbed vaccine ([0.5 mL) as an IM injection in the deltoid muscle on Day 1/Week 1.

4.4.2.2 23-Valent Pneumococcal Polysaccharide Vaccine

The 23-PPV is indicated for immunization against pneumococcal disease caused by those pneumococcal serotypes included in the vaccine. It has been chosen for this study to assess antibody production for a clinically relevant antigen that is unknown to most individuals. The 23-PPV will be administered in the deltoid muscle as a single IM injection.

Group A patients will receive the 23-PPV vaccine (0.5 mL) as an IM injection in the deltoid muscle at Day 112/Week 16.

Group B patients will receive the 23-PPV (0.5 mL) as an IM injection in the deltoid muscle at Day 28/Week 4.

4.4.2.3 Keyhole Limpet Hemocyanin

KLH is a high molecular weight respiratory metalloprotein found in the hemolymph of many mollusks and crustaceans. However, KLH does not have regulatory approval and is not marketed. Therefore, it may be considered an investigational medicinal product (IMP) in some regions. KLH has been used in global clinical trials as a challenge agent to evaluate patient's immune responses to neo-antigen (Mestecky et al. 2005; Miller et al. 2005; Spazierer et al. 2009). In this study, KLH will be used to test primary humoral response following B-cell depletion with OCR.

Group A patients will receive subcutaneously (SC) administered KLH (1 mg) at Day 85/Week 12, Day 112/Week 16, and Day 140/Week 20.

Group B patients will receive SC administered KLH (1 mg) at Day 1/Week 1, Day 28/Week 4, and Day 56/Week 8.

4.4.2.4 Conjugate Pneumococcal Vaccine

This study will assess antibody production when administered as 13-PCV booster vaccine after 23-PPV vaccine. The 13-PCV is indicated as active immunization for the prevention of pneumonia and invasive disease caused by 13 *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). It has been chosen for this study to assess antibody production when administered as 13-PCV booster vaccine after 23-PPV vaccine (the response to serotype 6A will not be tested in the assay used in this study). Booster 13-PCV will be administered in the deltoid muscle as a single IM injection.

Group A1 patients will receive the 13-PCV at Week 20/Day 140. Refer to the label for dosing and administration guidance.

4.4.2.5 Seasonal Influenza Vaccine

The influenza vaccine is indicated for immunization against influenza caused by the influenza strains included in the vaccine. The inactivated (or recombinant) vaccine has

been chosen for this study to assess antibody production for a commonly used clinically relevant antigen.

Group A2 patients can receive the influenza vaccine at any time between Day 85/Week 12 and Day 140/Week 20.

Group B patients will receive the influenza vaccine as an IM injection in the deltoid muscle at any time between Day 1/Week 1 and Day 84/Week 12. If a patient needs to receive the influenza vaccine after Week 12, the optional OCR infusion must be delayed.

Group A1 patients can receive the influenza vaccine at any time at the discretion of the investigator.

Refer to the label for dosing and administration guidance.

4.4.3 Investigational Medicinal Product Accountability

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipt and disposition of the study drug must be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following:

- Documentation of drug shipments received from the Sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patient.

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was administered
- The date[s] and quantity of the study drug administered to the patient

All records and drug supplies must be available for inspection/accountability by the monitor at every monitoring visit.

4.4.3.1 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate study drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

The study pharmacist should keep all OCR vials to measure compliance.

4.4.4 Destruction of the Investigational Medicinal Product

Local or institutional regulations may require immediate destruction of used IMP for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction. Written documentation of destruction must contain the following:

- Identity (batch numbers or medication numbers) of IMP destroyed
- Quantity of IMP destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed the IMP

Wherever possible, preferably drug should be destroyed locally on site according to their local policies and procedures once drug accountability has been completed by the monitor.

4.5 POST-TRIAL ACCESS TO OCRELIZUMAB

The Sponsor will offer continued access to OCR free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive OCR after completing the study if all of the following conditions are met:

- *The patient has a life-threatening or severe medical condition and requires continued OCR treatment for his or her well-being*
- *There are no appropriate alternative treatments available to the patient*
- *The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive OCR after completing the study if any of the following conditions are met:

- *OCR is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- *The Sponsor has discontinued development of OCR or data suggest that OCR is not effective for MS*
- *The Sponsor has reasonable safety concerns regarding OCR as treatment for MS*
- *Provision of the OCR is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.6 CONCOMITANT THERAPY

4.6.1 Definition of Concomitant Treatment

A concomitant medication is any drug or substance taken during the study, including the screening period. Over-the-counter medications and preventative vaccines received during the study are considered concomitant medications.

Concomitant medications will be reported at each visit in the relevant electronic Case Report Forms (eCRFs) starting from the baseline visit (including medication and procedures taken between screening and baseline).

4.6.2 Treatment for Symptoms of Multiple Sclerosis

The investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. Note: Patients in Group B can continue on IFN-β treatment that should be maintained at a stable dose as much as possible. During the OOE, initiation of therapy with dalfampridine (Fampyra/Ampyra) is allowed, if indicated by the treating physician.

4.6.3 Treatment of Relapses

Patients who experience a relapse during Immunization Study Period or the OOE may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted, 1 g/day IV methylprednisolone for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such patients should not discontinue the treatment period solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal (see Section 4.8).

4.6.3.1 Prohibited Therapy

Therapies for MS noted in the exclusion criteria under “Exclusions Related to Medications” (Section 4.1.2) are not permitted during the Immunization Study Period with the exception of systemic corticosteroids for the treatment of a relapse.

After patients have finished the treatment with OCR, they may receive alternative treatment for their MS as judged clinically appropriate by the investigator. However, as sufficient data are not available to inform regarding risks associated with switching to other products, the following recommendations are given:

- Caution is advised while patients remain B-cell depleted.

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

When patients begin an alternative treatment for MS, they will be discontinued from the study.

4.6.4 Immunizations

Physicians are advised to review the immunization status of patients who are considered for treatment with OCR and follow local/national guidance for adult vaccination against infectious disease. Known dates of immunizations will be recorded on specific eCRF pages, i.e., 'Vaccination History'. Immunizations (excluding tetanus-containing vaccines, 23-PPV, influenza, and 13-PCV) should be completed at least 6 weeks prior to first administration of OCR.

Patients who require de novo hepatitis B vaccination (three separate doses of vaccine) should also have completed the course at least 6 weeks prior to the first infusion of study drug.

The safety of immunization with live or live-attenuated vaccines following OCR therapy has not been studied. Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, *bacille Calmette-Guérin*, typhoid, yellow fever, vaccinia, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended within 6 weeks of first dosing (see Section 4.1.2), during OCR treatment, and for as long as the patient is B-cell depleted.

Patients who are eligible for a yearly influenza vaccine or who require immunizations or boosters for other diseases can receive immunization with killed/toxoid vaccines consistent with normal clinical practice.

For details regarding vaccinations during OCR treatment, please refer to the current version of the Ocrelizumab Investigator's Brochure.

4.7 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.7.1 Informed Consent Forms and Screening Log

All patients must sign and date the most current Institutional Review Board (IRB)/Institutional Ethics Committee's approved written informed consent before any study-specific assessments or procedures are performed.

Patients who consent to participate in this study will enter the 4-week screening period to be evaluated for eligibility. For details please refer to the Appendix 1. Patients must fulfill all entry criteria for participation in the study.

The screening period can be extended to a total period of 8 weeks in cases when a laboratory blood test needs to be repeated for confirmation during the screening interval, if a live vaccine must be administered by the patient's physician, or for other relevant clinical, administrative, or operational reasons.

Please note that based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or elected centers to exclude TB, Lyme disease, HAM, AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

An Eligibility Screening Form that documents the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

Each patient screened must be registered in the IxRS by the investigator or the investigator's research staff at screening. A screen failure record must be maintained by the investigator, and reasons for screen failure must be captured in the IxRS.

The medical record should state that the patient is participating in this clinical study.

4.7.2 Procedures for Enrollment of Eligible Patients

Once a patient has fulfilled all eligibility criteria, he or she will be randomized via IxRS to one of two treatment groups:

- Group A: OCR 600 mg (given as 300 mg × 2, 14 days apart)
- Group B: control group

Patient eligibility information will be provided to the IxRS by the investigator or the investigator's research staff at randomization. The patient will be randomized and assigned a unique treatment box number (medication number) and randomization number. As confirmation, the site will be provided with a verification of each patient's randomization.

The patient randomization numbers will be generated by Roche or its designee.
The patient randomization numbers are to be allocated sequentially in the order in which the patients are enrolled according to the specification document agreed with the external randomization company/center.

Treatment with the first study drug infusion should occur within 24 hours of randomization for patients in Group A. In exceptional cases where all baseline assessments cannot be completed within 24 hours, the first study drug infusion can be

administered within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing. In particular, there should be no evidence of an ongoing infection at the time of dosing.

No patient may begin treatment prior to randomization and assignment of a medication number.

4.7.3 Overview of Clinical Visits during the Immunization Study Period and the Optional Ocrelizumab Extension Period

After the screening visit, patients who fulfill the entry criteria will be scheduled for baseline assessments. Randomization will occur only after the patient meets all inclusion and exclusion criteria on Day 1. Visits will take place as described in Appendix 1.

Visits should be scheduled with reference to the date of the baseline visit (Day 1). A minimum interval of 20 weeks should be kept between the second infusion of OCR in Dose 1 (i.e., infusion Week 2) and the single infusion of Dose 2 (Week 24). For subsequent single infusions, a minimum of 22 weeks should be maintained between each infusion.

At infusion visits, patients treated with OCR should remain in observation for at least 1 hour after the completion of the infusion. If for logistical reasons the OCR infusion cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the patient still meets re-treatment criteria.

Patients who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be re-scheduled for a delayed dosing visit (see Section 4.7.4). Additional unscheduled visits for the assessment of potential relapses, new neurological symptoms, or safety events may occur at any time.

4.7.4 Safety Follow-Up

Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start treatment with commercial OCR, they will be discontinued from the SFU and from the study. SFU visits will be performed at 12-week intervals.

A dedicated (scheduled or unscheduled) safety follow-up visit directly prior to the start of an alternative MS treatment is required in order to assess the patient's clinical status and safety parameters. Additionally, an MRI scan should be performed within 4 weeks prior to the start of an alternative MS treatment (unless MRI has already been performed within prior 8 weeks; for details on assessments, Appendix 1).

4.7.5 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in Schedule of Assessments (Appendix 1). Thus, a patient who had all assessments of a dosing visit performed, but could not receive his/her infusion, should be re-scheduled for the infusion. For patients in Group A, delayed-dosing visits should not be scheduled for the first infusion of the first treatment (Dose 1 Infusion 1 on Day 1), as treatment with the first study drug infusion should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing; see Section 4.7.3).

In unforeseen situations, if the infusion of the first treatment dose (Day 1) is delayed for patients in Group A, then the visit for the second infusion should be scheduled 14 days after the delayed first infusion (±2 days). At the delayed-dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted.

4.7.6 Unscheduled Visits

Patients who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible regardless of the treatment group to which they were randomized, regardless of the dates of their pre-planned, scheduled study visits, and regardless of the study period. Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient.

Please refer also to Section 5.1.5.1 for guidance on the diagnosis of PML.

4.7.7 Withdrawal Visits

At the moment a patient meets one or more of the withdrawal criteria (Section 4.8.2), the patient will be regarded as withdrawn from treatment. Patients who withdraw from OCR treatment will need to complete all assessments as shown in Appendix 1 and will enter the SFU. Patients in Group B who do not receive an infusion of OCR in the OOE will not enter SFU.

After entering the SFU, if patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start treatment with commercial OCR, they will be discontinued from the SFU and from the study.

All patients will undergo a complete final evaluation according to the 'Withdrawal from Treatment Visit' in the Schedule of Assessments (Appendix 1). Thereafter, all patients will be treated according to individual center practice.

For patients who have withdrawn from the Immunization Study Period or the OOE or who are not eligible for treatment with OCR, the investigator should decide on further treatment of the underlying disease.

However, as sufficient data are not available to inform risks associated with switching to other products, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cladribine, daclizumab, cyclophosphamide, azathioprine, etc.), are strongly discouraged for as long as the patient remains B-cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection) (see also Section 4.6.3.1 for recommendations on alternative treatments for MS).

Please note: at the withdrawal from the Immunization Period or the OOE Period for patients in Groups A and B, an MRI scan will be required only if not performed in the prior 4 weeks.

4.7.8 Safety

Adverse events, vital signs, weight, physical and neurological examinations, clinical laboratory tests (including pregnancy tests), 12-lead ECGs, and data on concomitant medications and diseases will be collected throughout the study.

4.7.8.1 Medical History and Demographic Data

Relevant medications taken for the treatment of MS and medications taken for the symptoms of MS prior to the baseline visit will be recorded at screening.
Additionally, any relevant medications and medical/surgical procedures administered for any non-MS condition prior to the baseline visit will be recorded at screening.

4.7.8.2 Vital Signs

On the infusion days, the vital signs should be taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, the vital signs should be obtained prior to the study drug infusion, then every 15 minutes (±5 minutes) for the first hour; then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion.
On immunization days, vital signs should be taken prior to immunization.
On non-infusion/non-immunization days, the vital signs may be taken at any time during the visit. Additional vital signs readings may be taken at the discretion of the investigator in the event of an IRR or if clinically indicated and should be recorded on the unscheduled vital signs eCRF.

4.7.8.3 Electrocardiogram

A 12-lead ECG should be taken at the visits indicated in Appendix 1. Comments generated automatically by the ECG machine should not be recorded in the eCRF unless confirmed by a physician. An ECG is also required if the patient prematurely withdraws from the study.

4.7.8.4 Physical Examination

The physical examination will be performed as per Appendix 1. Diagnosis of new abnormalities or clinically significant worsening of pre-existing abnormalities should be recorded as adverse events if appropriate.

4.7.8.5 Brain Magnetic Resonance Imaging

Brain MRI scans will be obtained in all patients prior to baseline and annually as indicated in Appendix 1. It is recommended that patients be assessed as eligible for the trial (i.e., meet other study entrance criteria, where possible) prior to performance of the MRI scan.

The annual MRIs should be carried out as close as possible within a year of the baseline MRI performed at study entry. It can be performed at an unscheduled visit or be carried out at a scheduled visit. It is recommended that the MRI is performed at the visit scheduled 2 weeks prior the next OCR infusion (Visit q22), where retreatment criteria are assessed. To reduce the burden of additional visits for Group B patients, the scheduling of the annual MRI can be adapted to the pre-infusion visit schedule starting from the first annual MRI after the baseline MRI.

In patients receiving corticosteroids for an MS relapse, there should be an interval of 3 weeks between the last dose of corticosteroids and the scan.

An MRI scan should be performed within 4 weeks prior to the start of an alternative MS treatment (unless an MRI has already been performed within prior 8 weeks; see Section 4.6.3.1).

At the withdrawal from treatment visit, an MRI scan will be required only if not performed in the prior 4 weeks.

4.7.8.6 Neurological Examination

A neurological examination will be performed at every planned visit and at unscheduled visits in which a physical examination is performed.

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). A brain MRI scan and cerebrospinal fluid (CSF) analysis may be warranted to assist in the diagnosis of PML. See Section 5.1.5.1 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurological symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Section 5.1.5.1). The Sponsor's Medical Monitor should be contacted by email. In addition, the Sponsor's Medical Monitor should be immediately contacted by phone.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.5.1).

4.7.8.7 Telephone Interviews

The purpose of this semi-structured interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit.
The telephone interview will be conducted by site personnel familiar with the patient(s) every 4 weeks (±3 days) between the study visits throughout all periods and the SFU until 48 weeks after the last infusion of OCR.

The site will record in the eCRF the date of interview or if the site was unable to contact the patient. The documentation of the interview will be maintained in the patient's study file and all relevant safety information recorded in the eCRF. See Appendix 2 for the semi-structured telephone interview.

4.7.9 Laboratory Assessments

All laboratory samples collected during the study, with the exception of urine pregnancy tests, which will be analyzed locally, will be shipped to a Central Laboratory.

The procedures for the collection, handling, and shipping of laboratory samples are specified in the Laboratory Manual. The samples for this study should be classified, packed and shipped as UN3373 Biological Substance, Category B.

Full details of the central laboratory sample handling, shipment and reporting of results will be described in the Laboratory Manual.

4.7.9.1 Standard Laboratory Assessments

Further details will be provided in Laboratory Manual.

Hematology: hemoglobin, hematocrit, RBC, WBC (absolute and differential), ANC, and quantitative platelet count.

Blood chemistry: AST/SGOT, ALT/SGPT, γ glutamyl transferase, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, calcium, phosphorus, LDH, creatine phosphokinase, and triglycerides.

Thyroid function test: thyroid stimulating hormone will be tested at screening. Thyroid autoantibodies will be assayed at screening.

Flow cytometry will include (but is not limited to) the following cells:

- Total B cells (CD19 positive)

- B-cell subsets:
  - Memory B cells (CD19 positive, CD27 positive, CD38 negative)
  - Naïve B cells (CD19 positive, CD27 negative, IgD positive)
  - Plasmablasts ($CD19_{low}$, CD27 positive, $CD38_{high}$)
- Total T cells (CD3 positive)
- T-helper cells (CD3 positive, CD4 positive)
- TCTL (CD3 positive, CD8 positive)
- NK cells (CD3 negative, CD16/56 positive)

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

Anti-drug antibodies (ADA): Serum samples will be collected for determination of antibodies against OCR. Since OCR concentrations affect the ADA assay, the concentration of OCR will be measured as well at all timepoints with ADA assessment to enable interpretation of the results (pharmacokinetic [PK] sample). For details, please refer to Appendix 1.

Pregnancy Test: All women of childbearing potential must have regular pregnancy tests. At screening, a serum pregnancy test will be performed in the central laboratory. A urine pregnancy test (sensitivity of at least 25 mIU/mL β-hCG) will be performed locally at the timepoints shown in Appendix 1. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone infusion. A positive urine pregnancy test should be confirmed with a serum test through the central laboratory prior to any further dosing with OCR.

Please note: additional laboratory tests will be performed at screening in order to verify eligibility criteria. Please refer to Appendix 1 for further details.

4.7.9.2 Immunization Response Laboratory Assessments

Tetanus Antibody Assay

The tetanus antibody test will be used to measure anti-tetanus antibody levels in human serum samples. The tetanus antibody test is an ELISA that uses TT as a capturing reagent and alkaline phosphatase-conjugated anti-human IgG (γ) for detection. Results are reported in IU/mL.

Pneumococcal Antibody Assay (for 23-PPV and 13-PCV)

A bead-based multi-analyte immunodetection (MAID) assay using Luminex Magplex microspheres will be used to measure anti-pneumococcal IgG levels in human serum samples. The pneumococcal antibody assay is a fluoroimmunoassay that uses a Luminex Multiplex platform. Purified capsular polysaccharides isolated from 23 serotypes of S. pneumonia covalently attached to microbeads will be used as capturing reagent (IgG levels to serotype 6A, specific to 13-PCV cannot be tested in this assay). Results are reported in microgram of IgG/mL.

KLH Antibody Assay

A KLH antibody assay will be used to measure anti-KLH antibody levels (IgG and IgM) in human serum samples. The KLH antibody assay is an ELISA format using KLH as the plate coating and anti-human IgG-horseradish peroxidase for detection. Results are reported in titer units.

Influenza Vaccine

The hemagglutination inhibition (HAI) assay will be used to measure anti-influenza antibody levels in human serum samples. Results are reported in HAI units.

4.7.9.3 Hepatitis Screening and Liver Function Monitoring

Patients with recurrent or chronic hepatitis B or history/presence of hepatitis C infection must be excluded from enrollment into the study (see Section 4.1.2). In addition, hepatitis B and C serology will be performed at screening. Patients who have a positive result to either HBsAg, or total HBcAb associated with positive viral DNA titers as measured by PCR, or a positive result for HepCAb should be excluded from the trial. Patients with evidence of past resolved hepatitis B infection (i.e., positive total HBcAb associated with a negative viral DNA) can be enrolled, and will have the hepatitis B viral DNA checked regularly as per Appendix 1. Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment.

These patients will not receive further infusions of OCR and will enter the SFU. Liver function (i.e., ALT/SGPT, AST/SGOT, γ glutamyl transferase, alkaline phosphatase, total bilirubin) should be reviewed throughout the study. Patients who develop evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded. Patients who develop hepatitis B or C should be withdrawn from the study and should enter the SFU. Should treatment be prescribed, this will be recorded in the eCRF. Patients with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after recovery. Please refer also to Section 5.3.5.7 for further guidelines on liver function monitoring.

4.7.9.4 Pharmacokinetic Assessments

Blood samples will be collected to evaluate the trough concentrations.

For all infusion visits, a blood sample should be taken 5–30 minutes before the methylprednisolone infusion and as indicated in the Schedule of Assessments (Appendix 1). At other times (non-infusion visits), samples may be taken at any time during the visit.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual, which will be provided to each site.

4.7.10 Optional Ocrelizumab Extension Period

The OOE starts on Dose 2 (600 mg, single infusion) for patients in Group A and as 2 × 300 mg single infusions for patients in Group B.

In order to verify re-treatment criteria for infusions in the OOE, patients should attend a scheduled visit 2 weeks prior to an infusion visit (the first visit will be added prior to Dose 3 for patients in Group A and prior to Dose 2 [600 mg single infusion] for patients in Group B).

Additional unscheduled visits for safety events may occur at any time. Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient.

Refer to Appendix 1 for study procedures at OOE and unscheduled visits.

4.8 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.8.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

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 form. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.8.2 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. Patients must be withdrawn from treatment (regardless of whether they are in the Immunization Study Period or the OOE) under the following circumstances:

- Life threatening (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) infusion-related event that occurred during a previous OCR infusion
- Patients who demonstrate active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B
- Patients with PML
- Patients who decide to discontinue the treatment
- The investigator decides that discontinuation of treatment is in the best clinical interest of the patient

Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start treatment with commercial OCR, they will be discontinued from the SFU and from the study.

If the patient discontinues from the study, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient withdrew from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without their consent.
The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure, after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure, or for any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF. If possible, the patient should be followed until the adverse event has resolved.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

Please note: It is important to distinguish between withdrawal from treatment and withdrawal from study. *Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start treatment with commercial OCR, they will be discontinued from the SFU and from the study.*

Upon withdrawal from the study, any untested routine samples will be destroyed. However, information already obtained from samples up until the time of withdrawal will be used.

4.8.3 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab was approved in the U.S. on 28 March 2017 under the trade name Ocrevus® for the treatment of patients with RMS and PPMS, and in Canada on 14 August 2017 for the treatment of patients with RRMS. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below. For the most recent information regarding identified and potential risks associated with ocrelizumab, please refer to the current version of the Ocrelizumab Investigator's Brochure.

5.1.1 Identified Risks and Adverse Drug Reactions Associated with Ocrelizumab Use

5.1.1.1 Infusion-Related Reactions

For this study, an IRR is defined as an event that occurs during or within 24 hours after the end of the infusion and which can be reasonably assumed as being related to study medication.

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab in order to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of

an infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to: pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia *and anaphylaxis*.

Some of these events have been severe enough to warrant interruption or discontinuation of the infusion. Symptoms are often reversible if the infusion is interrupted and/or patients receive additional treatment with an antihistaminic, acetaminophen, epinephrine, or an IV corticosteroid.

Patients should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR and should 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 infusion. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

In this study, patients will be pre-medicated with IV methylprednisolone (100 mg) and an antihistamine, an antipyretic drug is also recommended to prevent IRRs.

5.1.1.2 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%–6%, simplex and zoster) than with comparators (approximately 3%).

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

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

See Section 4.7.9.3 for hepatitis screening and monitoring of liver function.

Delay OCR administration in patients with an active infection until the infection is resolved. Physicians should exercise caution when considering the use of OCR in patients with underlying conditions that may predispose patients to serious infection. Patients who develop signs/symptoms of infection while participating in this trial should be seen immediately, samples should be taken for appropriate microbiological analysis, and appropriate treatment should be initiated promptly.

For PML, see potential risk below.

Patients should be screened for TB according to national guidelines. As with other infections, patients with active TB should not be enrolled; patients with latent TB should be treated prior to enrollment.

Patients should be warned that the risk of infection may be increased by exposure to the medications to be used in this study and should be asked to contact the clinic staff if they start to develop signs of infection.

5.1.1.3 Decrease in Immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total Igs over the controlled period of the studies, mainly driven by reduction in IgM. The proportion of patients with decrease in Igs below LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out (see Section 5.1.1.4 and the Ocrelizumab Investigator's Brochure for further details).

5.1.1.4 Serious Infections Related to Decrease in Immunoglobulins (Particularly in Patients Previously Exposed to Immunosuppressive or Immunomodulary Drugs or with Preexisting Hypogammaglobulinemia)

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

5.1.1.5 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) and is an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion is from 51 patients in Study WA21493 and indicates that the median time to B-cell repletion (returned to baseline or LLN, whichever occurred first) of B cells was 72 weeks (range: 27–175 weeks).

5.1.1.6 Impaired Response to Vaccination

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

In the Immunization Study Period of this Study BN29739, the humoral responses to tetanus toxoid (TT), 23-valent pneumococcal polysaccharide (23-PPV), keyhole limpet hemocyanin (KLH) neoantigen, and seasonal influenza vaccines were decreased in RMS patients treated with OCR (compared with those patients not treated with OCR) at all timepoints measured. Nevertheless, RMS patients who received OCR and were peripherally B-cell depleted were able to mount humoral responses, albeit decreased, to clinically relevant vaccines (TT, 23-PPV, influenza) and the neoantigen KLH. The results of the study confirm the current recommendation that patients should complete local vaccination requirements 6 weeks prior to initiation of OCR to obtain full effectiveness of the vaccines. In addition, for seasonal influenza vaccines, it is still recommended to vaccinate patients receiving OCR, as a humoral response to the vaccine, even if attenuated, can be expected.

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

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab.

The safety of immunization with live or live-attenuated viral vaccines following ocrelizumab therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended while B cells are depleted. Please see Section 4.6.4 for guidance on immunization.

5.1.2 Potential Risks Associated with Ocrelizumab Use

5.1.2.1 Progressive Multifocal Leukoencephalopathy

PML is a potentially fatal neurological condition linked to reactivation of a polyomavirus (John Cunningham virus [JCV]) and active viral replication in the brain. Polyomavirus infection is acquired in childhood and up to 80% of adults demonstrate serological

evidence of past infection. Reactivation of JCV replication with transient viremia or viruria unassociated with clinical symptoms may occur spontaneously in healthy persons. Less frequently, CNS symptoms associated with active viral replication in brain tissue are observed. The clinical syndrome is significantly more frequent among immune-suppressed patients. There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Berger 2014).

PML is an important potential risk for ocrelizumab. It has been reported in patients receiving ocrelizumab but only in patients where other contributory factors were present, such as prior immunosuppressive treatment (e.g., natalizumab or fingolimod). Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms, as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for JC viral DNA, and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Please refer to the current Ocrelizumab Investigator's Brochure for further details.

Healthcare professionals should be alerted to the early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms as these can be similar to an MS relapse. Please refer to Section 5.1.5.1 for guidance on the diagnosis of PML.

If PML is suspected, a neurological consultation should be obtained and treatment suspended until PML has been ruled out.

If PML is confirmed in a patient who has received OCR, no further infusions should be administered and the patient will be withdrawn from treatment (see Section 4.8) and enter the SFU period of the study.

PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor.

5.1.2.2 Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although not typically 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 an infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

5.1.2.3 Malignancies, Including Breast Cancer

An increased risk of malignancy with OCR may exist. In controlled trials in MS, malignancies, including breast cancer, occurred more frequently in OCR-treated

patients. Breast cancer occurred in 6 of 781 females treated with OCR and none of 668 females treated with INF-beta-1a (Rebif®) or placebo.

Patients should follow standard breast cancer screening guidelines.

5.1.2.4 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 events were mild to moderate in severity. Approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. *Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.*

In case the ANC decreases below the exclusionary level of 1.5 x $10^3/\mu L$, further administration of OCR should be suspended until resolution of this laboratory abnormality or held indefinitely (as per the Re-treatment criteria, Section 4.1.4).

5.1.3 Risks Associated with Corticosteroids

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

5.1.4 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.

5.1.5 Management of Specific Adverse Events

5.1.5.1 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

The following safety monitoring algorithm (Figure 3) will be implemented in this study.

Comprehensive neurological assessments will be performed at each planned and unscheduled visit that a physical examination is performed, and all patients will be required to undergo a neurological exam for calculation of an EDSS at baseline and if PML is suspected. This requires that Functional System Score (FSS) also be determined. The examination to calculate the FSS includes cognitive, visual and motor assessments, the neurological systems most often affected by PML, as well as assessments of other neurological systems.

In the eCRF, the investigator will record the presence or absence of neurological deficits localized to the cerebral cortex (e.g., cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis), cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination), at each visit. Presence of such neurological findings will be recorded as adverse events. If a diagnosis for the

deficits is identified, the symptoms should be replaced by the diagnosis in the adverse event eCRF.

Patients will undergo a telephone interview between the study visits by site personnel familiar with the patient(s). The purpose of this interview is to identify and collect information on any changes in the patient's health status, including new or worsening neurological symptoms, that warrant an unscheduled visit (Appendix 1). Partners or caregivers of study patients, if applicable, will be informed on symptoms and signs that may be suggestive of PML and should be instructed to contact the site, should any such signs or symptoms appear.

In the event that new or worsening neurological symptoms are considered during the telephone interview, a neurological evaluation will be conducted. Should a non-MS etiology, such as PML, be considered, further assessments should be done. The evaluation of PML may include a brain MRI scan and CSF analysis per the proposed treatment algorithm (see Figure 3).

The following clinical guidance is provided:

Treatment of relapse and other neurological symptoms:

- As in all MS studies, new or recurrent neurological symptoms that occur in study patients should prompt careful clinical evaluation.
- Anti-CD20 antibodies have been associated with PML. A risk of PML cannot be ruled out. PML should be considered in patients who develop worsening neurological signs or symptoms.
- There are no pathognomonic signs or symptoms that distinguish MS from PML, but there are certain clinical features that may help differentiate between the two conditions (see Table 1 and Table 2).
- In addition to PML and MS, other CNS conditions (e.g., stroke, migraine) should be considered when evaluating a patient with new neurological changes.
- Relapses should be managed according to the study protocol.
- Corticosteroid treatment should only be considered for cases in which PML is unlikely on clinical grounds and when the severity of the relapse warrants such treatment. Lack of response to corticosteroids should trigger further investigation.

Action steps if PML is suspected:

- If the clinical presentation is suggestive of PML, further investigations should include brain MRI evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 3) a lumbar puncture with evaluation of the CSF for the detection of JCV DNA using a validated sensitive 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.

Please note: In the event that PML is suspected, additional blood, urine, and CSF samples should be obtained for JCV analysis. CSF samples will be analyzed upon receipt and the results will be provided directly to the investigational site and to the Sponsor. The additional blood and urine samples will be stored up to 1 year after LPLV in the study. For details, please refer to the most up-to-date laboratory manual providing storage conditions and shipment instructions.

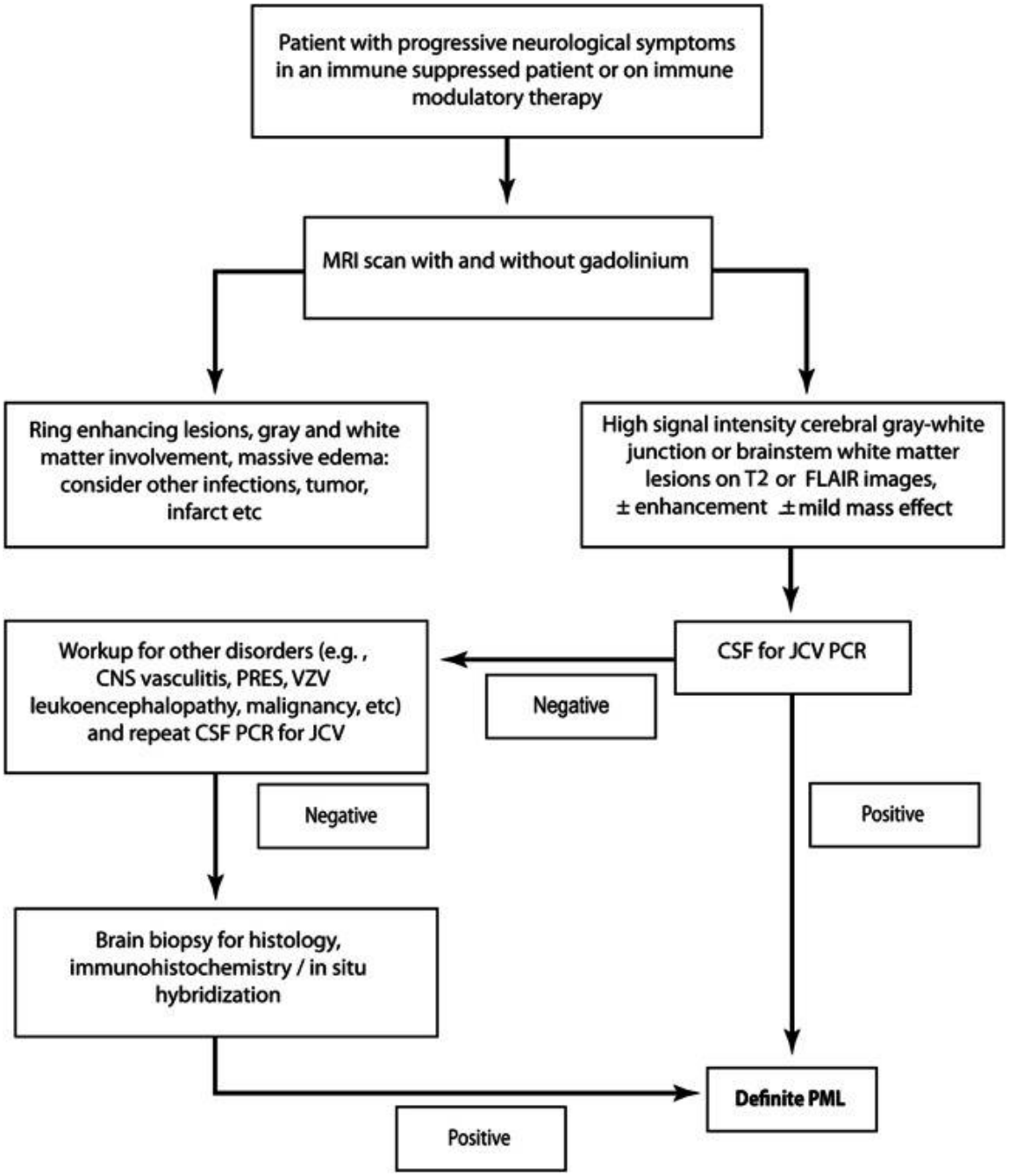
MRI assessment:

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2- and T1-weighted sequences, with and without Gd, should be performed to assess patients with neurological changes suggestive of PML (see Figure 3)
- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 1 and Table 2 for differences in lesion characteristics that may help differentiate between PML and MS).

CSF assessment:

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

Figure 3 Diagnostic Algorithm Framework for PML (Berger et al. 2013)



CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; JCV = John Cunningham virus; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella zoster virus.

Table 1 Clinical Features to Distinguish between Multiple Sclerosis Relapse and Progressive Multifocal Leukoencephalopathy

	MS Relapse	PML
Onset	Acute	Subacute
Evolution	Over hours to days Normally stabilizes Resolves spontaneously or with treatment	Over weeks Progressive
Clinical presentation	Diplopia Paresthesia Paraparesis Optic neuritis Myelopathy	Cortical signs and symptoms Behavioral and neuropsychological alterations Retrochiasmal visual deficits Hemiparesis Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Table 2 Magnetic Resonance Imaging Lesion Characteristics Typical of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy

Feature	MS Relapse	PML
Location of new lesions	Mostly focal; affect entire brain and spinal cord, in white and possibly gray matter	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; irregular in shape; confined to white matter; sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal; lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious; true extension of abnormality more clearly visible than in T2-weighted images

Table 2 Magnetic Resonance Imaging Lesion Characteristics Typical of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy (cont.)

Feature	MS Relapse	PML
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement, even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy.
Atrophy	Focal atrophy possible due to focal white-matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.5.1).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH 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), except as described in Section 5.3.5.9

- 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 the National Cancer Institute [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).

The exception to this definition of a serious adverse event is in the rare event that a patient is hospitalized following an MS relapse, as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone. The rationale for this

exception is that some countries and/or clinical sites routinely hospitalize patients who require administration of methylprednisolone in the event of an MS relapse. Thus, the serious adverse event criteria for "hospitalization" would be met on the basis of local practice and would not reflect the seriousness of the event.

When the MS relapse results in hospitalization for any reason other than for routine treatment of the relapse (such as for a treatment course beyond the standard treatment described in Section 4.6.3) or when hospitalization is prolonged, the MS relapse should be considered a serious adverse event.

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 include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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.

New or worsening neurological symptoms not considered MS-related should be recorded on an adverse event page and the monitor should be informed.

After informed consent has been obtained **but prior to initiation of study treatments**, 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 treatments, all adverse events will be reported until Week 48 of the SFU Period. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see 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 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not 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:

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

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 ocrelizumab 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 and their associated details should be recorded on the dedicated IRR eCRF page. Investigators should consider a local IRR for any symptoms affecting the skin, and localized to only one place. Any other IRR should be considered as systemic.

5.3.5.2 Diagnosis versus Signs and Symptoms

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 × 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 if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should

be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

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

5.3.5.8 Deaths

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

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 Hospitalization or Prolonged Hospitalization

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

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 respite care
- Planned hospitalization required by the protocol

- 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

An event that leads to hospitalization under the following circumstance is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, 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).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted] M.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur After Study Drug Initiation

After initiation of study drug, serious adverse events, and adverse events of special interest will be reported until Week 48 of the SFU Period.

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 Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

The pregnancy outcome and the health status of the child will be followed until the child is 1 year of age. Data collection is voluntary only; it does not include any interventions or invasive procedures. A Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire will be submitted to Health Authorities and IRB/IECs for their approval, along with the infant data release consent form. For more information on the Infant Health Questionnaire, please refer to the latest version of the Infant Health Questionnaire Guidance document.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 48 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

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

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, 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 documents:

- Ocrelizumab Investigator's Brochure
- Keyhole Limpet Hemocyanin (KLH) Summary of Product Characteristics

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. The Sponsor will not be expediting reporting of any adverse events related to the vaccines (i.e., TT, pneumococcal polysaccharide, conjugate pneumococcal booster and influenza) administered in this study to health authorities as all vaccines used within this study are non-Sponsor non-IMPs.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting (please refer to the current Ocrelizumab Investigator’s Brochure).

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 100 patients will be enrolled using a 2:1 randomization ratio into active (Group A) and control (Group B) groups. For the positive response to TT-containing adsorbed vaccine measured 8 weeks after the administration of vaccine, if both the control and active (OCR) groups have 70% response rates, the expected half width of the resulting 95% CI of the difference of two response rates is 0.201.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of subjects who are randomized, treated and have completed the study will be tabulated by treatment group. Reasons for premature study withdrawal will be summarized and listed by treatment group. Key eligibility criteria violations and other major protocol deviations will be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Treatment groups will be compared with respect to demographics (e.g., age, sex, and race/ethnicity) and baseline characteristics measured on Day 1 (e.g., body weight, background corticosteroid usage, years since prior vaccinations and pre-vaccination levels). Results will be summarized by treatment group using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables.

6.4 IMMUNOLOGY ENDPOINTS

6.4.1 Analysis of Immunology Endpoints

Primary Endpoint

The proportion of patients with positive responses to TT vaccine measured 8 weeks after administration of the TT vaccine for Group A and Group B will be assessed.

For patients with pre-immunization tetanus antibody titers < 0.1 IU/mL, a positive response to the booster immunization is defined as an antibody titer ≥ 0.2 IU/mL measured 8 weeks after the immunization. For patients with pre-immunization tetanus antibody titers ≥ 0.1 IU/mL, positive response to the booster immunization is defined as a 4-fold increase in antibody titer measured 8 weeks after the immunization. Pre-vaccination levels are those obtained immediately prior to receipt of a vaccine.

Secondary Endpoints

All secondary endpoints are as defined in Section 3.4.2. Descriptive statistical analyses will be used to compare the proportion of patients with responses in the assessments and groups as specified in that section. The mean level of antibody parameters will be presented using geometric means.

Exploratory analyses will be performed to assess the possible relationship among measurements, and clinical response and will be specified in the statistical analysis plan.

6.5 SAFETY ANALYSES

All subjects who received any amount of OCR or any vaccine will be included in the safety analyses and will be analyzed according to the treatment received.

6.5.1 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be mapped to thesaurus terms. Adverse events will be tabulated by body system and treatment group. Adverse events will also be summarized by maximum intensity for each treatment group (Groups A and B). Separate summaries will be provided for serious adverse events, treatment–related adverse events, and adverse events leading to study withdrawal.

6.5.2 Laboratory Tests

Descriptive summaries of laboratory values and changes from Day 1 and throughout the study will be generated. The proportion of patients who experience treatment-emergent laboratory abnormalities will be compared between groups.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis will be conducted with all ocrelizumab concentration versus time data from the Immunization Study Period, plus all PK data from the OOE and SFU period available at the time of the PK analysis. All patients who have measurable concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation. The PK data of this study may be pooled with more extensive data from other studies. The PK analysis will be reported separately from the main CSR.

Trough concentrations of ocrelizumab at all time-points of ADA sampling will be reported as part of the immunogenicity/ADA listings in the CSR.

6.7 INTERIM ANALYSIS

An interim analysis will not be conducted.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored 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 have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/Ethics Committee (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, 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, patient 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws.

8.2 INFORMED CONSENT

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

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

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or

clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible

for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

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 study will be sponsored by Roche. Approximately 100 patients are expected be enrolled in this study; approximately 30–35 centers will participate in the study in the United States and Canada. Patients will be enrolled and randomized using an IxRS. A central laboratory will be used for all laboratory assessments with the exception of urine pregnancy tests. Any remaining PK or ADA samples may be used for exploratory experiments for PK and ADA assay development purposes and additional safety assessments (e.g., JCV testing in case of a confirmed PML diagnosis) as appropriate. These remaining samples will be stored for up to 5 years following database closure.

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 *Study Information* at the following Web site:

http://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).

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Appendix 1 Schedule of Assessments: Tables A–C

TABLE A: SCHEDULE OF ASSESSMENTS FOR IMMUNIZATION STUDY PERIOD AND OPTIONAL OCRELIZUMAB TREATMENT PERIOD FOR GROUP A (A1 AND A2)

	Group A (A1 and A2)												
	Screening[1]	**Immunization Study Period**						**OOE[2,3]**			**WD from Treatment**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (unless noted) (Window)	**-28 to -1**	**1 (BL)[1]**	**15 (±2 d)**	**85 (±4 d)**	**112 (±4 d)**	**140 (±4 d)**	**169[2] (±4 d)**	**169[2] (±4 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**1**	**2**	**12**	**16**	**20**	**24**	**24**	**q22 w[3]**	**q24 w[3]**			
↓ = OCR infusion		↓	↓					↓		↓			
Informed consent[6]	x												
Medical history, MS history, prior and concomitant treatments	x												
Eligibility review	x	x						x		x			
Physical and neurological exam	x	x	x		x	x	x	x		x	x	x	x
Vital signs[7]	x	x	x	x	x	x	x	x		x	x	x	x
12-lead ECG[8]	x	x	x				x	x		x	x		
Height	x												
Weight	x							x[9]		x[9]	x		
EDSS[10]		x											

Appendix 1 Schedule of Assessments: Table A (cont.)

	Group A (A1 and A2)												
	Screening[1]	**Immunization Study Period**						**OOE[2,3]**			**WD from Treatment**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (unless noted) (Window)	**-28 to -1**	**1 (BL)[1]**	**15 (±2 d)**	**85 (±4 d)**	**112 (±4 d)**	**140 (±4 d)**	**169[2] (±4 d)**	**169[2] (±4 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**1**	**2**	**12**	**16**	**20**	**24**	**24**	**q22 w[3]**	**q24 w[3]**			
MRI (once annually [±4 w]) [11]	x										x		
Adverse events/MS relapse	Only SAEs[12]	x	x	x	x	x	x	x	x	x	x	x	x
Telephone interview				Every 4 weeks[13]									
Concomitant treatments		x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[14]	x	x	x	x	x	x	x	x		x	x	x	x
ADA[15]		x				x	x	x	x	x	x		
PK sampling[16]		x	x	x	x	x	x	x		x	x		
FSH[17]	x												
Hepatitis screening[18]	x												
HBV DNA monitoring[19]		x		x			x	x	x		x		
RPR	x												

Appendix 1 Schedule of Assessments: Table A (cont.)

	Group A (A1 and A2)												
	Screening[1]	**Immunization Study Period**						**OOE[2,3]**			**WD from Treatment**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (unless noted) (Window)	**-28 to -1**	**1 (BL)[1]**	**15 (±2 d)**	**85 (±4 d)**	**112 (±4 d)**	**140 (±4 d)**	**169[2] (±4 d)**	**169[2] (±4 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**1**	**2**	**12**	**16**	**20**	**24**	**24**	**q22 w[3]**	**q24 w[3]**			
CD4 count[20]	x	x				x			x	x	x		
IgG subtype		x		x					x		x		
Total Ig, IgA, IgG, IgM	x	x		x			x	x	x		x		
Flow cytometry[21]		x	x	x	X	x	x	x	x	x	x		
Routine safety labs[22]	x	x	x	x	x	x	x	x	x	x	x	x	
Pretreatment with IV methylprednisolone and an antihistamine [23]		x	x					x		x			x
IV OCR[24]		x	x					x		x			x
Influenza vaccine[25]				I/M[25] → Influenza → post-vaccine assessment after 4 weeks									
KLH				I/M[26]	I/M[26]	I/M[26]	M	M[26]					

Appendix 1 Schedule of Assessments: Table A (cont.)

	Group A (A1 and A2)												
	Screening[1]	Immunization Study Period						OOE[2,3]			WD from Treatment	Unscheduled[4]	Delayed Dosing[5]
Study Day (unless noted) (Window)	**-28 to -1**	**1 (BL)[1]**	**15 (±2 d)**	**85 (±4 d)**	**112 (±4 d)**	**140 (±4 d)**	**169[2] (±4 d)**	**169[2] (±4 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**1**	**2**	**12**	**16**	**20**	**24**	**24**	**q22 w[3]**	**q24 w[3]**			
23-PPV					I/M[26]	M	M	M[26]					
13-PCV[27]						I/M[26]	M	M[26]					
TT-containing vaccine[28]				I/M[26]	M	M							

ADA=anti-drug antibodies; β-hCG=β-human chorionic gonadotropin; BL=baseline; CD4=cluster of differentiation; 13-PCV=Conjugate pneumococcal vaccine; d = day; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; FSH=follicle-stimulating hormone; I= immunization;; IV=intravenous;; KLH= Keyhole Limpet hemocyanin; M= measurement pre-immunization and/or post-baseline immunization assessment; OOE=Optional Ocrelizumab Extension Period; PK=pharmacokinetic; 23-PPV= 23-valent polysaccharide pneumococcus vaccine; RPR=rapid plasma reagin; SAE=serious adverse event; TT: Tetanus toxoid–containing vaccine; SC=subcutaneous; w=week; WD=withdrawal.

1 The Screening Period can be extended to a total period of 8 weeks in cases when a laboratory blood test needs to be repeated for confirmation during the screening interval, if a live vaccine must be administered by the patient's physician, or for other relevant clinical, administrative, or operational reasons.

2 The Immunization Study Period will end at Day 169 (Week 24). Assessments shown under Immunization Study Period should be performed on all patients. Assessments indicated in the OOE column should only be done if the patient chooses and is eligible to receive OCR.

3 Patients can continue to receive OCR (600 mg single infusion) at an interval of 24 weeks (minimum interval of 22 weeks).

4 **Unscheduled Visit:** assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. Other tests/assessments may be done as appropriate.

5 A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF form when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be done as appropriate.

Appendix 1 Schedule of Assessments: Table A (cont.)

6 **Informed Consent** will be obtained in written form from all patients at screening in order to meet eligibility for the study.

7 **Vital signs** will be obtained while the patient is in the semi supine position (after 5 minutes), i.e., pulse rate, systolic, and diastolic blood pressure, respiration rate, and temperature. On OCR infusion visits, the vital signs should be taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, vital signs should be obtained prior to the study drug infusion, then every 15 minutes (± 5 minutes) for the first hour; then every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. On immunization days, vital signs should be taken prior to immunization. On non-infusion/non-immunization days, the vital signs may be taken at any time during the visit.

8 **ECG (pre- and post-dose):** On infusion visits, ECG should be taken within 45 minutes prior to the methylprednisolone infusion in all patients, and within 60 minutes after completion of the OCR infusion. On non-infusion days, the ECG may be taken at any time during the visit.

9 Weight should be obtained prior to the OCR infusion.

10 The EDSS should be obtained at baseline (pre-dose). An EDSS should also be performed if PML is suspected

11 MRI should be done at Baseline and annually throughout the OOE period (±4-week window) as per Section 4.7.8.5. The annual MRIs in the OOE should be carried out as close as possible within a year of the baseline MRI performed at study entry. It can be performed at an unscheduled visit or be carried out at a scheduled visit, e.g., at the visit scheduled 2 weeks prior to the next OCR infusion (Visit q22), where retreatment criteria are assessed. Please note: at the withdrawal from Immunization Period or OOE Period, an MRI scan will be required only if not performed in the prior 4 weeks.

12 After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

13 **Telephone interview:** The telephone interview will be conducted by site personnel familiar with the patient(s) every 4 weeks (± 3 days) between the study visits throughout all periods and the SFU until 48 weeks after the last infusion of OCR. The telephone interview is done to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit. See Appendix 2 for the semi-structured telephone interview.

14 **Pregnancy test:** Serum β-hCG must be performed at screening in women of childbearing potential. Subsequently, urine β-hCG [sensitivity of at least 25 mIU/mL] will be done. On infusion and immunization visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of child-bearing potential. If positive, do not dose and confirm with a serum pregnancy test.

15 **ADA**: On infusion visits, samples are collected prior to the methylprednisolone infusion.

16 **PK samples:** On infusion visits, a blood sample should be taken before the methylprednisolone infusion and on infusion visits at Weeks 1, 2, and 24 an additional sample within 30 minutes after the end of the OCR infusion. At other times (non-infusion visits), samples may be taken at any time during the visit.

17 **FSH**: FSH only applicable to women to confirm the post-menopausal status at screening.

18 **Hepatitis screening**: to be eligible, all patients must have negative a negative HepCAb, a negative HBsAg result and either negative HBcAb or a positive HBcAb but negative HBV DNA.

19 **Hepatitis B virus DNA monitoring**. For those eligible patients enrolled with positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

Appendix 1 Schedule of Assessments: Table A (cont.)

20 **CD4 count**: will be measured separately at screening, and be included in the flow cytometry (FACS) panel at all following visits including every q22-week visit in order to inform eligibility/re-treatment criteria. Other re-treatment labs will be measured as part of IgG and routine safety labs (see item 21 and 22).

21 **Flow cytometry**: including CD19 and other circulating B-cell subsets, T-cells (including CD4 cells), NK cells and other leukocytes. On the infusion days, samples should be collected prior to infusion of methylprednisolone.

22 **Routine safety labs**. On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

23 All patients will receive **prophylactic treatment** with 100 mg of methylprednisolone IV 30 minutes prior to, and an IV or oral antihistamine such as diphenhydramine 50 mg 30–60 minutes prior to OCR infusions. In patients where methylprednisolone is contraindicated, corresponding doses of other IV steroids (e.g., dexamethasone) may be used as premedication. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g), 30–60 minutes prior to OCR infusions.

24 **Study drug administration**: The investigator must review the clinical and laboratory re-treatment criteria prior to re-dosing patients with study drug at Day 168 (Week 24) and prior to any subsequent OCR infusion.

25 Influenza vaccine and post-vaccination assessment for Group A2 only. Influenza can be administered between Weeks 12–20. Post-vaccine assessments must be done after 4 weeks. For patients in Group A2 who are due to receive the influenza vaccine during their country-specific influenza vaccine blackout period, administration of the vaccine should be given prior to the start of this blackout period. Group A1 patients can receive the influenza vaccine at any time at the discretion of the investigator.

26 M = Sample to be taken prior to immunization on days when vaccines are administered. On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

27 Group A1 only.

28 TT-containing adsorbed vaccine refers to the combined tetanus and diphtheria (Td/DT) or tetanus, diphtheria, and acellular pertussis (DTaP/Tdap) vaccines.

Appendix 1 Schedule of Assessments: Table B

TABLE B: SCHEDULE OF ASSESSMENTS FOR IMMUNIZATION STUDY PERIOD AND OPTIONAL OCRELIZUMAB TREATMENT PERIOD

	Group B													
	Screening[1]	**Immunization Study Period**				**OOE[2,3]**						**WD from Treatment[4]**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (Unless Noted) Window	**-28 to -1**	**1**	**28 (±4 d)**	**56 (±4 d)**	**84[1] (±4 d)**	**84[1] (±4 d)**	**98 (±2 d)**	**238 (±4 d)**	**252 (±2 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**–**	**4**	**8**	**12**	**12**	**14**	**34**	**36**	**q22 w[3]**	**q24 w[3]**			
↓ = OCR infusion						↓	↓		↓		↓			
Informed consent[6]	x													
Medical history, MS history, prior and concomitant treatments	x													
Eligibility review	x	x				x			x		x			
Physical and neurological examination	x	x				x	x		x		x	x	x	x
Vital signs[7]	x	x	x	x	x	x	x		x		x	x	x	x
12-lead ECG[8]	x	x				x	x		x		x	x		
Height	x													

Appendix 1 Schedule of Assessments: Table B (cont.)

	Group B													
	Screening[1]	**Immunization Study Period**				**OOE[2,3]**						**WD from Treatment[4]**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (Unless Noted) Window	**-28 to -1**	**1**	**28 (±4 d)**	**56 (±4 d)**	**84[1] (±4 d)**	**84[1] (±4 d)**	**98 (±2 d)**	**238 (±4 d)**	**252 (±2 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**–**	**4**	**8**	**12**	**12**	**14**	**34**	**36**	**q22 w[3]**	**q24 w[3]**			
Weight[9]	x					x			x		x	x		
EDSS[10]		x												
MRI (once annually [±4 w])[11]	x											x		
Adverse events	Only SAEs[12]	x	x	x	x	x	x	x	x	x	x	x	x	x
Telephone interview			Every 4 weeks[13]											
Concomitant treatments		x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[14]	x	x	x	x	x	x	x		x		x	x	x	x
ADA[15]						x	x	x	x	x	x	x		
PK samples[16]						x	x		x		x	x		
FSH[17]	x													
Hepatitis screening[18]	x													

Appendix 1 Schedule of Assessments: Table B (cont.)

	Group B													
	Screening[1]	**Immunization Study Period**				**OOE[2,3]**						**WD from Treatment[4]**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (Unless Noted) Window	**-28 to -1**	**1**	**28 (±4 d)**	**56 (±4 d)**	**84[1] (±4 d)**	**84[1] (±4 d)**	**98 (±2 d)**	**238 (±4 d)**	**252 (±2 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**–**	**4**	**8**	**12**	**12**	**14**	**34**	**36**	**q22 w[3]**	**q24 w[3]**			
HBV DNA[19] monitoring		x			x	x		x	x	x		x		
RPR	x													
CD4 count[20]	x					x		x	x	x	x	x		
IgG subtype		x[21]			x[21]	x[21]		x		x		x		
Total Ig, IgA, IgG, IgM	x	x	x	x	x	x		x		x		x		
Flow cytometry[22]		x			x	x	x	x	x	x	x	x		
Routine safety labs[23]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pretreatment with IV methylprednisolone and an antihistamine[24]						x	x		x		x			x
IV OCR[25]						x	x		x		x			x

Appendix 1 Schedule of Assessments: Table B (cont.)

	Group B													
	Screening[1]	**Immunization Study Period**				**OOE[2,3]**						**WD from Treatment[4]**	**Unscheduled[4]**	**Delayed Dosing[5]**
Study Day (Unless Noted) Window	**-28 to -1**	**1**	**28 (±4 d)**	**56 (±4 d)**	**84[1] (±4 d)**	**84[1] (±4 d)**	**98 (±2 d)**	**238 (±4 d)**	**252 (±2 d)**	**q22w (±4 d) (-2 w prior to q24 w)**	**q24 w[3] (±2 w)**			
Week	**-4 to -1**	**–**	**4**	**8**	**12**	**12**	**14**	**34**	**36**	**q22 w[3]**	**q24 w[3]**			
Influenza[26]		M[26] → Influenza → +4 weeks M												
KLH		I/M[27]	I/M[27]	I/M[27]	M	M[27]								
23-PPV			I/M[27]	M	M	M[27]								
TT-containing vaccine[28]		I/M[27]	M	M										

ADA=anti-drug antibodies; β-hCG=β-human chorionic gonadotropin; BL=baseline; CD4=cluster of differentiation; 13-PCV-23= Conjugate pneumococcal vaccine; ECG=electrocardiogram; eCRF=electronic case report form; EDSS=Expanded Disability Status Scale; FSH=follicle-stimulating hormone; I= immunization; IV=intravenous; KLH= Keyhole Limpet hemocyanin; M= measurement pre-immunization and/or post-baseline immunization assessment;; OOE=Optional Ocrelizumab Extension Period; PK=pharmacokinetic; 23-PPV= 23-valent polysaccharide pneumococcus vaccine; RPR=rapid plasma reagin; SAE=serious adverse event; TT: Tetanus toxoid-containing vaccine SC=subcutaneous; w=week.

1 The screening period can be extended to a total period of 8 weeks in cases when a laboratory blood test needs to be repeated for confirmation during the screening interval, if a live vaccine must be administered by the patient's physician, or for other relevant clinical, administrative, or operational reasons.

2 The Immunization Study Period will end at Day 84 (Week 12). Assessments shown under Immunization Study Period should be performed on all patients. Assessments indicated in the OOE column should only be done if the patient chooses and is eligible to receive OCR.

3 Patients can continue to receive OCR (600 mg, single infusion) at an interval of 24 weeks (minimum interval of 22 weeks).

Appendix 1 Schedule of Assessments: Table B (cont.)

4 **Unscheduled Visit:** assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. Other tests/assessments may be done as appropriate.

5 A delayed dosing visit will be performed and recorded in the Delayed Dosing Visit eCRF form when dosing cannot be administered at the scheduled dosing visit. Other tests or assessments may be done as appropriate.

6 **Informed Consent** will be obtained in written form from all patients at screening in order to meet eligibility for the study.

7 **Vital signs** will be obtained while the patient is in the semi supine position (after 5 minutes), i.e., pulse rate, systolic, and diastolic blood pressure, respiration rate, and temperature. On OCR infusion visits, the vital signs should be taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, vital signs should be obtained prior to the study drug infusion, then every 15 minutes (± 5 minutes) for the first hour; then every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. On immunization days, vital signs should be taken prior to immunization. On non-infusion/non-immunization days, the vital signs may be taken at any time during the visit.

8 **ECG (pre- and post-dose):** On infusion visits, ECG should be taken within 45 minutes prior to the methylprednisolone infusion in all patients, and within 60 minutes after completion of the OCR infusion. On non-infusion days, the ECG may be taken at any time during the visit.

9 Weight should be obtained prior to the OCR infusion.

10 The EDSS should be obtained at baseline (pre-dose). An EDSS should also be performed if PML is suspected.

11 MRI should be done at Baseline and annually throughout the OOE Period, **(±4-week window)** as per Section 4.7.8.5. The annual MRIs in the OOE should be carried out as close as possible within a year of the baseline MRI performed at study entry. It can be performed at an unscheduled visit or be carried out at a scheduled visit, e.g , at the visit scheduled 2 weeks prior the next OCR infusion (Visit q22), where retreatment criteria are assessed. To reduce the burden of additional visits for Group B patients, the scheduling of the annual MRI can be adapted to the pre-infusion visit schedule starting from the first annual MRI after the baseline MRI. Please note: at the withdrawal from treatment visits, an MRI scan will be required only if not performed in the prior 4 weeks.

12 After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

13 **Telephone interview**: A semi-structured telephone interview will be done on a 4-week (± 3 days) basis between visits from Week 5 to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit. See Appendix 2 for the semi-structured telephone interview.

14 **Pregnancy test:** Serum β-hCG must be performed at screening in women of childbearing potential. Subsequently, urine β-hCG [sensitivity of at least 25 mIU/mL] will be done. On infusion and immunization visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of child-bearing potential. If positive, do not dose and confirm with a serum pregnancy test.

15 **ADA**: On infusion visits, samples are collected prior to the methylprednisolone infusion.

Appendix 1 Schedule of Assessments: Table B (cont.)

16 **PK samples:** On infusion visits, a PK blood sample should be taken before the methylprednisolone infusion and on infusion visits at Weeks 12, 14, and 36 an additional sample within 30 minutes after the end of the OCR infusion. At other times (non-infusion visits), samples may be taken at any time during the visit.

17 **FSH**: FSH only applicable to women to confirm the post-menopausal status at screening.

18 **Hepatitis screening**: to be eligible, all patients must have negative a negative HepCAb, a negative HBsAg result and either negative HBcAb or a positive HBcAb but negative HBV DNA.

19 **Hepatitis B virus DNA monitoring**. For those eligible patients enrolled with positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

20 **CD4 count**: will be measured separately at screening, and be part of the flow cytometry (FACS) panel at all following visits, including every q22w visit in order to inform eligibility/re-treatment criteria. Other re-treatment labs will be measured as part of IgG and routine safety labs (see item 20).

21 **IgG subtypes**: sample to be taken prior to immunization and /or OCR infusion.

22 **Flow cytometry**: including CD19 and other circulating B-cell subsets, T-cells (including CD4 cells), NK cells and other leukocytes. On the infusion days, samples should be collected prior to infusion of methylprednisolone.

23 **Routine safety labs**. On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

24 All patients will receive **prophylactic treatment** with 100 mg of methylprednisolone IV 30 minutes prior to, and an IV or oral antihistamine such as diphenhydramine 50 mg 30–60 minutes prior to OCR infusions. In patients where methylprednisolone is contraindicated, corresponding doses of other IV steroids (e.g., dexamethasone) may be used as premedication. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to OCR infusions.

25 **Study drug administration**: The investigator must review the clinical and laboratory re-treatment criteria prior to dosing patients with study drug at Day 84 (Week 12) and prior to every subsequent OCR infusion.

26 Influenza vaccine for Group B: Influenza can be administered between Weeks 1 and 12. For patients who need to receive the influenza vaccine after Week 12, the OCR infusion must be delayed. Post-vaccine assessments must be done after 4 weeks. For patients in Group B who are due to receive the influenza vaccine during their country–specific influenza vaccine blackout period, administration of the vaccine should be given prior to the start of this blackout period

27 M = Sample to be taken prior to immunization on days when vaccines are administered. On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

28 TT-containing adsorbed vaccine refers to the combined tetanus and diphtheria (DT/Td) or tetanus, diphtheria, and acellular pertussis (DTaP/Tdap) vaccines.

Appendix 1 Schedule of Assessments: Table C

TABLE C: SCHEDULE OF ASSESSMENTS FOR SAFETY FOLLOW-UP PERIOD (ALL PATIENTS)

	Safety Follow-Up[1,8]	End of Observation or withdrawal from Safety Follow-Up[1]
Assessment	**Visits every 12 weeks (±7 days)**	
Flow cytometry[2]	x	x
Telephone follow-up[3]	x	
Urine pregnancy test	x	x
Routine safety labs[4]	x	x
Total Ig, IgA, IgG, IgM	x[5]	x
ADA[6]	x[5]	x
IgG subtype	x[5]	x
HBV DNA[7]	x	x
Vital signs	x	x
Physical and neurological examination	x[5]	x
Adverse events	x	x
Concomitant treatments	x	x

DNA=deoxyribonucleic acid; ADA= anti-drug- antibodies.

Appendix 1 Schedule of Assessments: Table C (cont.)

1 **Safety Follow-Up:** *Patients who discontinue treatment early for any reason and patients who complete the study treatment period will be followed up for 48 weeks after the last infusion of OCR. When patients begin an alternative treatment for MS (see Section 4.6.3.1 on prohibited therapies), or start commercial OCR, they will be discontinued from the SFU and from the study.*

2 **Flow cytometry:** including CD19 and other circulating B-cell subsets, T cells, NK cells, and other leukocytes.

3 A **semi-structured telephone interview** will be conducted by site personnel familiar with the patient(s) every 4 weeks (± 3 days) between the study visits throughout all periods and the SFU until 48 weeks after the last infusion of OCR. See Appendix 2 for the semi-structured telephone interview.

4 Routine safety labs: hematology and chemistry.

5 Needs to be assessed only every 24 weeks.

6 ADA: two serum samples are required.

7 Hepatitis monitoring: hepatitis to be monitored only in patients with screening results of HBsAg negative, HBcAb positive, and HBV DNA negative, inclusive (HBcAb test to be done every 24 weeks).

8 A dedicated (scheduled or unscheduled) safety follow-up visit directly prior to the start of an alternative MS treatment is required for patients who begin an alternative treatment for MS while in safety follow-up in order to assess the patient's clinical status and safety parameters.

Appendix 2
Telephone Interviews

The purpose of this interview is to identify any new or worsening neurological symptoms that warrant an unscheduled visit and to collect data on possible events of infections.

Telephone interviews should be performed by study personnel every 4 weeks between clinic visits.

Please ask the following questions and record patient's answers during the Telephone Interview:

Questions: No / Yes

1. Since your last visit or telephone interview, have you had any new or worsening medical problems (such as sudden changes in your thinking, alterations in your behavior, visual disturbances, extremity weakness, limb coordination problems, or gait abnormalities) that have persisted over more than one day?
2. Since your last visit or telephone interview, have you had any signs of infection?
3. Since your last visit or telephone interview, have you had any other new or worsening medical problems or conditions (including pregnancy), surgery, or hospitalization?
4. Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat cancer or MS or any other new medicines that weaken your immune system or steroid medicines other than for the treatment of a recent relapse)?

If the patient answered YES to any question, contact the Investigator and review the patient's answers. The Investigator can determine if an unscheduled visit is required. Please record any relevant safety information in the appropriate eCRF form.

Record any pertinent comments made by the patient during the interview:

Patient ID:

_____

_____

_____

NAME:_____ Date:_____

Name of person completing the telephone interview