PROTOCOL	
TITLE:	**AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	MA30143
VERSION NUMBER:	*10*.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
NCT NUMBER:	NCT03085810
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. HOFFMANN-LA ROCHE LTD Grenzacherstrasse 124, 4070 Basel, Switzerland
DATE FINAL:	Version 1.0: 7 October 2016
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PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
23-Mar-2021 18:13:17	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 10.0: RATIONALE

Protocol MA30143 has been amended with the following key changes. Changes to the protocol, along with a rationale for each change, are summarized below.

Objectives and endpoints (Section 2)

Several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are currently approved and shown to be efficacious in preventing severe COVID-19 infection. However, evidence on the SARS-CoV-2 vaccine response in patients with multiple sclerosis (MS) treated with ocrelizumab is lacking. Thus, the exploratory objective to investigate the effect of ocrelizumab on antibody and T cell responses in patients vaccinated with SARS-CoV-2 vaccine has been added to Table 1 with a detailed rationale for the same in Section 3.3 and the details for this optional procedure in Section 4.5.13 and Figure 3.

Exploratory Objectives:	
• To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved SARS-CoV-2 vaccine	• Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine

Safety follow-up Period

Section 3.1.4 and Figure 2 have been updated 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 the study drug.

The requirement of additional safety follow-up until B-cell repletion (continued B-cell monitoring period) for patients whose B cells have not been repleted after 48 weeks of the safety follow-up has been removed on the basis that incidence of adverse events after 48 weeks during the safety follow-up period was low and similar to the incidence of adverse events in the ocrelizumab all-exposure population. No increased or new safety risks were identified during the B-cell monitoring period in any ocrelizumab study, so such monitoring in this population is unnecessary.

The requirement of safety follow-up for 48 weeks (regardless of B-cell count) for patients switching from ocrelizumab to alternative treatments for MS has been removed and it has been clarified that when patients begin an alternative treatment for MS, they will be discontinued from the study. No increased or new safety risks have been identified during such monitoring periods in any ocrelizumab study.

End of Study

Sections 3.1.3 and 3.2 have been updated to clarify that after the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24-week and 48-week confirmed disability progression (CDP/confirmed disability improvement [CDI] confirmation

visit). For those patients presenting with an Expanded Disability Status Scale (EDSS) change at the end of the treatment period and who roll over to the long-term extension (LTE) study LIBERTO (Study MN39158), the 24-week and 48-week CDP confirmation visits will occur during the LTE study (Study MN39158). For patients who discontinue the study (e.g., move onto commercial ocrelizumab, or start treatment with another disease modifying treatment [DMT]), the EDSS CDP confirmatory assessments will not be performed.

Inclusion Criteria (Section 4.1.1)

- Section 4.1.1 (Inclusion Criteria) has been updated to list the optional contraceptive methods which are considered highly effective.

Study Assessments

- The requirement of a structured telephone interview post ocrelizumab infusion to collect information on any possible infusion-related reactions (IRRs) or any other changes in the patient's health status which may have occurred after the discharge (previous Section 4.5.13) has been removed.
- Section 4.5.13 has been added to include the optional procedure of collecting blood samples for analysis of immune responses to SARS-CoV-2 vaccine.

Statistical considerations and analysis plan

- Section 6.4.1 has been updated to clarify that with respect to CDP confirmation visits, only EDSS data at all the visits occurring in the treatment period of the study and LTE study (for patients who roll over to study MN39158) will be used. Appropriate statistical methods to account for missing confirmation visits will be defined in the statistical analysis plan (SAP).
- Section 6.6: It has been added that exploratory immunology analyses of SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses will be analyzed as appropriate and details will be specified in a separate Biomarker Analysis Plan.

Appendix 1

Appendix 1 has been updated to reflect the changes in the protocol

Appendix 2

- Appendix 2 has been updated to reflect the changes in the protocol.
- Magnetic resonance imaging (MRI) and telephone follow-up (every 8 weeks) have been removed from the Schedule of Assessments during the follow-up period.

Appendix 3

The National MS EDSS has been replaced with Neurostatus

Appendix 7

The Infant Health Questionnaire (IHQ) has been replaced with the recent version (September 2020), which was updated to correct the inconsistencies noticed between the protocol Section 5.4.3.1 and the IHQ.

Appendix 8

- The safety follow-up period has been updated as per the main study.

Appendix 9

- The safety follow-up period has been updated as per the main study.
- The volume of additional blood samples in cases of relapse, de novo vaccination or severe infection has been corrected to 6 x 9 mL EDTA blood and 1 x 9 mL serum samples [total blood volume of 63 mL]).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

{Name}
{Address}

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS**
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NCT NUMBER:	NCT03085810
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

The main study will evaluate the effectiveness and safety of ocrelizumab in early stage relapsing-remitting multiple sclerosis (RRMS) patients. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the effectiveness of ocrelizumab in early stage of RRMS	• Evaluate clinical measures related to disease progression over 4 years in patients in the early stage of their RRMS disease
Overview of the effectiveness measures:	
• Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	**Related to disability progression**: • Time to onset of confirmed disability progression (CDP) sustained for at least 24 weeks and 48 weeks • Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and 48 weeks at year 1, 2 and 4 • Proportion of patients who have improved, stable or worsened disability compared with baseline measured by Expanded Disability Status Scale (EDSS) annually • Mean change from baseline in EDSS score over the course of the study **Other clinical measures and composite endpoints:** • Time to first protocol-defined event of disease activity • Time to first relapse • Annualized relapse rate

Objectives	Corresponding Endpoints
	• Proportion of patient relapse free by week 48, 96, 144 and 192 • Proportion of patients with no evidence of protocol-defined disease activity (NEDA) over week 96, week 144 and week 192 where disease activity is defined as at least one the following events: protocol-defined relapse; CDP based on increases in EDSS; a T1 Gadolinium (Gd)-enhanced lesion after Week 8; or a new and/or enlarging T2 hyperintense lesion on magnetic resonance imaging (MRI) after Week 8 compared to the Week 8 MRI scan. • Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20% increase in timed 25 Foot Walk Test [T25FWT]; 20% increase in timed 9 hole peg test [9HPT]) between baseline and week 96/192 • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion between baseline and week 96/192 • Change from baseline of Multiple Sclerosis Functional Composite (MSFC) and its composites (T25FW, 9HP, and Paced Auditory Serial Addition Test [PASAT]) over time • Change from baseline in cognitive performance as measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) performed annually **Related to MRI** • Total number of T1 Gd-enhancing lesions as detected by brain MRI over time • Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time • Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time • Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time **Other measures related to MS disease:** • Time to treatment discontinuation/switch **Patient reported outcomes:** • Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) • SymptoMScreen • Quality of life (Multiple Sclerosis Impact Scale [MSIS]-29)

Objectives	Corresponding Endpoints
Exploratory Objectives:	
• To further evaluate the effectiveness of ocrelizumab in early stage of RRMS	• Markers or predictors/indicators of disease progression (clinical and MRI markers) at week 24, week 48 and week 96 • Severity of relapses (hospitalization, use of corticosteroids, residual disability)
• To investigate the impact of ocrelizumab therapy on biomarkers associated *with* neurodegenerative mechanisms and/or other biomarkers in early stage RRMS	• Changes in levels of neurofilament light chain (NfL), levels of soluble neurodegeneration markers and/or other biomarkers in peripheral blood, serum or plasma
• *To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine*	• *Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine*
Safety Objective:	
• To evaluate the safety and tolerability of ocrelizumab in early stage of RRMS	• Rate and nature of adverse events • Changes in vital signs, physical and neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-multiple sclerosis [MS] central nervous system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)
Optional substudies in selected countries and at selected sites:	
T and B cells impact substudy in France 288 weeks longitudinal, multi-center, sub study (n=~50). Participating centers are restricted to French investigator centers with PBMC (peripheral blood mononuclear cell) technical and storage capacity.	• Impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients, indirect impact of ocrelizumab on B cell repopulation and relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab
Immune substudy in Germany and other selected countries (n=~80).	• Frequencies of circulating immune cell subsets (B cells, T cells, NK cells, antigen presenting cells)
Ocrelizumab shorter infusion substudy (approximately 700 patients: of which approximately 550 additional patients and approximately 150 currently participating in the main study)	• Proportion of patients with IRRs occurring during or within 24 hours following the first infusion after randomization to the shorter infusion substudy

Study Design

Description of Study

The main study is a prospective, multicenter, open-label, single-arm effectiveness and safety study in patients with early stage RRMS. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks (±14 days) for the remainder of the study duration.

The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 192 weeks (i.e. 24 weeks after the last dose of ocrelizumab, which will be administered at Week 168). Patients will be allowed to switch from the conventional ocrelizumab infusion (~3.5 hours) to the shorter ocrelizumab infusion (~2.0 hours) at any visit after the Week 24 visit based on the schedules of infusion as per the protocol, after providing written informed consent and in agreement with their treating physician, provided they have not experienced any previous serious infusion-related reactions (IRRs) with ocrelizumab treatment. While on the shorter infusion, the patients can switch back to the conventional infusion in agreement with their treating physician. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.
- A *safety* follow-up period of 48 weeks *after the last infusion of the study drug*, as explained below

Safety Follow-up Period: Patients who discontinue treatment early *for any reason and patients who complete the study treatment period and do not continue in a separate long-term extension (LTE) study,* will be followed up for 48 weeks after the last infusion of study drug. *When patients begin an alternative treatment for MS (see section 4.4.1 "Prohibited Therapy'), they will be discontinued from the study.*

Patients who discontinue study treatment and switch to commercially marketed ocrelizumab, either after completion of the 192 weeks Treatment Period or after early discontinuation of the 192 weeks Treatment Period, will not enter the safety Follow-up Period.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits (starting after the site visit at 8 weeks) during the treatment period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.

Number of Patients

The main study was initially planned to enroll at least 600 patients with early stage RRMS. Approximately 550 additional patients were to be enrolled in the shorter infusion substudy. They would also be enrolled in the main study (see Appendix 10 for more details). Therefore, the main study would enroll a total of at least 1,100 patients. A total of 1,225 patients (678 in the main study and 547 in the shorter infusion substudy) were enrolled in the study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18 – 55 years, inclusive
- Have a definite diagnosis of RRMS, as per the revised McDonald 2010 criteria (Polman et al. 2011)
- Have a length of disease duration, from first documented clinical attack consistent with MS disease of ≤ 3 years
- Within the last 12 months:

  One or more clinically reported relapse(s)

  OR

  One or more signs of MRI activity
- EDSS of 0.0 to 3.5 inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months or longer after the last dose of ocrelizumab as applicable in the ocrelizumab package leaflet.

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

The following are acceptable contraceptive methods (*failure rate >1%* as defined by the Clinical Trial Facilitation Group [CTFG] guidelines): *(1)* progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, *(2)* male or female condom with or without spermicide, *(3)* cap, diaphragm, or sponge with spermicide*, (4)* combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods).

Birth control methods that are highly effective (i.e. failure rate <1% [CTFG]) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomised partner; (7) sexual abstinence.

Exclusion Criteria

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

- Secondary progressive multiple sclerosis (SPMS) or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia, weight>140 kg, etc.)
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 [HTLV-1], herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease, sarcoidosis)
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Exclusions Related to General Health

- Pregnancy or lactation
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History or currently active primary or secondary immunodeficiency
- Lack of peripheral venous access

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks prior to screening or oral antibiotics 2 weeks prior to screening

  Note: Active infections should be treated and effectively controlled before possible inclusion in the study
- History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, progressive multifocal leukoencephalopathy [PML])
- History or known presence of recurrent or chronic infection (e.g., human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins
- History of alcohol or drug abuse within 24 weeks prior to baseline
- History or laboratory evidence of coagulation disorders

<u>Exclusions Related to Medications</u>

- Received any prior approved DMT with a label for MS, for example, interferons, glatiramer acetate, natalizumab, alemtuzumab, daclizumab, fingolimod, teriflunomide and dimethylfumarate.
- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit.

  In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks.
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency).
- Contraindications to or intolerance of oral or IV corticosteroids, including methylprednisolone administered IV, according to the country label, including:

  a) Psychosis not yet controlled by a treatment

  b) Hypersensitivity to any of the constituents.
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).
- Systemic corticosteroid therapy within 4 weeks prior to screening.
- Any previous treatment with immunosuppressants/ immunomodulators/ antineoplastic therapies (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, cladribine, mitoxantrone, laquinimod, total body irradiation, or bone marrow transplantation).
- Treatment with IV immunoglobulins (Ig) within 12 weeks prior to baseline.
- Treatment with investigational DMT
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- Treatment with fampridine/dalfamipridine (Fampyra®)/Ampyra®) unless on stable dose for ≥ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period.

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])
- Lymphocyte count below lower limit of normal (LLN)
- CD4 count<250/µL.
- Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)≥ 3.0 × the upper limit of normal (ULN)
- Serum creatinine >1.4 mg/dL (> 124 µmol/L) for women or > 1.6 mg/dL (> 141µmol/L) for men
- Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)
- Platelet count <100,000/µL (<100 × 10^9/L)
- Absolute neutrophil count <1.0 × 10^3/µL

*Re-testing before baseline: 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.

Please note: based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

End of Study

The end of the main study is defined as the last patient last visit *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*

The end of the study treatment period has been defined as the date on which the last patient receiving the full study treatment reached the 192 week visit. *After the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24week and 48week-CDP (CDP/CDI confirmation visit). For those patients presenting with an EDSS change at the end of the treatment period and who roll over to the LTE study LIBERTO (Study MN39158), the 24-week and 48-week CDP confirmation visits will occur during the LTE study (Study MN39158). For patients who discontinue the study (e.g., move onto commercial ocrelizumab, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.*

Length of Study

The total length of the main study, from screening of the first patient to the end of the study depends on the recruitment rate and is expected to be approximately *356* weeks (~7 years). This includes an enrolment period of 116 weeks.

Investigational Medicinal Products

Test Product (Investigational Drug)

The first dose of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg IV infusion in 500 mL 0.9% sodium chloride every subsequent doses (i.e., every 24 weeks ± 14 days) for a maximum of 8 doses.

Non-Investigational Medicinal Products

The following premedications must be administered prior to each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs):

- 100 mg intravenous methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion.
- Antihistamine via oral, intramuscular or IV route to be completed approximately 30-60 minutes and not less than 25 minutes prior to each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered).
- The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

Statistical Methods

Primary Analysis

The main study is an open-label single-arm study. No formal confirmatory hypothesis test will be conducted.

The intent-to-treat (ITT) population will include all enrolled patients who received any dose of ocrelizumab and will be used for the primary analyses of effectiveness and safety. The per-protocol (PP) population will include all ITT patients without major protocol deviations deemed to potentially affect the effectiveness endpoints. The PP population will be used for supportive effectiveness analyses. Safety population is defined as all enrolled patients who received any dose or part of a dose of ocrelizumab in the study. After the Week 192 visit of the last enrolled patient, approximately *24 weeks and* 48 weeks may be needed to allow the confirmation of the last event of the *24 week and* 48 week-CDP (CDP/CDI confirmation visit). The analysis will be performed after the last CDP and CDI confirmation visit. *With respect to CDP confirmation visits, only EDSS data at all the visits occurring in the treatment period of the study and LTE study (for patients who roll over to study MN39158) will be used. Appropriate statistical methods to account for missing confirmation visits will be defined in the statistical analysis plan (SAP).*

The evaluation of the clinical effectiveness of ocrelizumab will be based upon the events and assessments in-between the baseline and week 192.The MRI activity will be evaluated from week 8 (baseline for MRI-based endpoints) to week 192. For the patients who do not have an event, time-to-event endpoints will be censored at the time of last visit in the study. A descriptive analysis based on the Kaplan-Meier method will be performed for the time to CDP and other time-to-event endpoints, such as the time to first relapse or to first event of disease activity. Change of EDSS from baseline at week 192 will be analyzed based on mixed models for repeated measures. Details will be specified in the SAP.

Determination of Sample Size

Sample size considerations for the main study are based on pooled data from two ocrelizumab phase III trials in RRMS (OPERA I and II). Based on extrapolations from these studies, we can conservatively expect 15% of patients (or less) to have a CDP event and approximately the same number of patients to be censored (including the patients who drop out during the study) by week 192. In this case, for 1,100 patients, the precision (half-width of the 95% confidence interval) of the estimated CDP rate by study end is expected to be approximately 1.8% i.e., the 95% confidence interval will be (13.2%, 16.8%). In OPERA the EDSS improvement at 2 years had a standard deviation of 0.74, based on 240 patients from the ocrelizumab group, who were previously treatment-naïve with disease duration ≤3 years and EDSS ≤3.5. The standard deviation was rather stable over time and is assumed to remain stable after four years of treatment. A sample size of 1,100 patients is expected to provide a precision for the estimate of the EDSS change from baseline of about 0.037, assuming a standard deviation of 0.75. Assuming no EDSS change from baseline to week 196, with 1,100 patients, the 95% confidence interval will be (-0.074, 0.074).

The main study was initially planned to enroll at least 600 patients. Approximately 550 additional patients were to be enrolled in the shorter infusion substudy. They would also be enrolled in the main study (see Appendix 10 for more details). Therefore, the main study would enroll a total of at least 1,100 patients. A total of 1,225 patients (678 in the main study and 547 in the shorter infusion substudy) were enrolled in the study.

Interim Analyses

Exploratory analyses of selected endpoints (including CDP and safety analysis) will be performed during the course of the study, for example, after all patients have completed the first 48 weeks of the treatment phase and the necessary data are available.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AIDS	Acquire immunodeficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARR	Annual relapse rate
AST	Aspartate aminotransferase
β-hCG	Beta subunit human chorionic gonadotropin
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BRC	Biological Resource center
BVMT-R	Brief Visuospatial Memory Test Revised
CCOD	Clinical cut-off date
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CI	Confidence interval
CNS	Central nervous system
CRO	Contract research organization
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CVLT-II	California Verbal Learning Test 2
DMT	Disease modifying treatment
DRB	Data Review Board
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion-recovery
FSH	Follicle stimulating hormone
FSS	Functional Systems Score
GA	Glatiramer acetate
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	Gamma-glutamyl transpeptidase
GPA	Granulomatosis with polyangiitis
HAM	HTLV-1 associated myelopathy

Abbreviation	Definition
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HEENT	Head, eye, ear, nose, and throat
HIV	Human immunodeficiency virus
9HPT	9 Hole peg test
HR	Hazard ratio
HTLV-1	Human T-lymphotropic virus 1
IA	Interim analysis
IB	Investigator's brochure
ICH	International Conference on Harmonisation
iDCC	Independent Data Coordinating Center
iDMC	Independent Data Monitoring Committee
IFN-β	Interferon beta
IFNg	*Interferon gamma*
Ig	Immunoglobulin
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	intent-to-treat
IV	Intravenous
IxRS	Interactive voice/Web response system
JCV	John Cunningham virus
LLN	Lower limit of normal
LPLV	Last patient, last visit
LTE	Long term extension
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
MMRM	Mixed model with repeated measure
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSIS-29	Multiple Sclerosis Impact Scale (29-item scale)
NCI	National Cancer Institute
NEDA	No evidence of disease activity
NEP	No evidence of progression
NEPAD	No evidence of progression or active disease
NfL	Neurofilament light chain
NGS	Next generation sequencing
NYHA	New York Heart Association
OCB	Oligoclonal band

Abbreviation	Definition
ON	Optic neuritis
PASAT	Paced Auditory Serial Addition Test
PBMC	*Peripheral blood mononuclear cells*
PCR	Polymerase chain reaction
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Per-protocol
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
PRO	Patient-reported outcome
PY	Patient years
QOL	Quality of life
RA	Rheumatoid arthritis
RBC	Red blood cell
RBR	Research Biosample Repository
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus 2*
SD	Standard deviation
SDMT	Symbol digit modalities test
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIs	Serious infections
SPMS	Secondary progressive multiple sclerosis
TB	Tuberculosis
T25FWT	Timed 25 foot walk test
ULN	Upper limit of normal
U.S.	United States
USP	United States Pharmacopeia
WBC	White blood cell
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
WPAI	Work productivity and activity impairment questionnaire

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3 million worldwide (Tullman et al. 2013). MS primarily affects young adults, with 70%–80% of patients having an age of onset (i.e., initial visit to a physician) between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002), and has a strong gender bias, with approximately 64%–70% of diagnosed patients being women (Goodin 2014).

MS is subcategorized into three main phenotypes of the disease course: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS; Lublin et al. 201455T); approximately 85% of MS patients initially present with RRMS (Confavreaux et al. 2000; Leray et al. 2015). The majority of RRMS patients will transition into SPMS within 20-25 years (Trojano et al. 2003).

The clinical signs in MS can occur in isolation or in combination, and can include weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasescu et al. 2014). Current diagnosis of definite MS involves both clinical (history and neurological exam) and paraclinical (for example, Magnetic Resonance Imaging [MRI], Spinal Tap, Evoked potentials) evidence. The revised 2010 McDonald MRI criteria for demonstration of lesion dissemination of space include ≥1 T2 lesion in at least two of the following four areas of the CNS: periventricular, juxtacortical, infratentorial, and spinal cord; and demonstration of lesion dissemination in time include the following: a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI; and simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time (Polman et al. 2011).

MS treatments tackle separately the acute exacerbations and their prevention. Symptomatic management of relapses involves the use of corticosteroids, while disease-modifying treatments (DMTs) aim to decrease the clinical relapse rate and concomitant inflammation within the CNS (Tanasescu et al. 2014). DMTs, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs, are used to slow the development of MS-related neurological damage and disability progression. By providing a more effective approach to MS treatment, DMTs may improve quality of life for individuals with MS (Weinstock-Guttman 2013).

The therapeutic landscape of MS is changing rapidly. After several years in which first-line DMTs – glatiramer acetate (GA) and interferon beta (IFNβ) – constituted the principal treatment options, a variety of new agents for MS treatment are now approved by regulatory authorities or in phase II and III clinical trials (Tanasescu et al. 2014). In

2004 natalizumab was approved for relapsing forms of MS and in 2014, alemtuzumab and peg IFNβ-1a. Fingolimod was the first oral DMT approved by Food and Drug Administration (FDA) in 2010 for relapsing forms of MS (RMS) followed by teriflunomide in 2012 and dimethyl fumarate in 2013 (wwww.mymsaa.org).

Suppression of disease activity and disability progression as early as possible remains an important goal of therapy in MS (Noyes and Weinstock-Guttman 2013; Ziemssen et al. 2015). With the emergence of more efficacious therapies and a better understanding of the consequences of subclinical and early disease activity, physicians have a lower tolerance for allowing disease activity to persist because what is lost in MS cannot typically be regained. The potential risk of irreversible disease progression is therefore an important factor in the therapeutic decision making of patients and their physicians. Although there are now several approved therapies for RMS, some lack sufficient efficacy to quell progression of disability (Coles et al. 2008), while more effective therapies are often reserved for later use because of serious risks (Ziemssen et al. 2015). Thus there remains a need for highly effective therapies with a benefit-risk profile that supports its expeditious use at any time during the course of disease to preserve CNS tissue and neurological function, stem accrual of irreversible disability, and improve the quality of life for people living with MS.

1.2 BACKGROUND ON OCRELIZUMAB

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

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

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

Summary of Clinical Studies of Ocrelizumab in MS

In two double-blind, double-dummy Phase III global RMS trials (Studies WA21092 and WA21093), ocrelizumab 600 mg demonstrated superior efficacy over subcutaneous IFNβ-1a 44 μg (Hauser et al. 2015). Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints. Ocrelizumab 600 mg demonstrated statistically significant superiority compared with IFNβ-1a on each of the following major efficacy endpoints:

- Relative reductions of 46% and 47% (both $p < 0.0001$) in the protocol-defined annual relapse rate (ARR) in Studies WA21092 and WA21093, respectively (primary endpoint)
- A 40% relative reduction in both the 12-week confirmed disability progression [CDP] (Hazards ratio [HR] 0.60 [95% confidence interval [CI]: 0.45, 0.81], $p = 0.0006$) and 24-week CDP (HR 0.60 [95% CI: 0.43, 0.84], p=0.0025) in the pooled analysis of Studies WA21092 and WA21093. Each individual trial also demonstrated a significant relative risk reduction of 12-week CDP and 24-week CDP (43% reduction for both 12- and 24-week CDP in Study WA21092 and 37% reduction for both 12- and 24-week CDP in Study WA21093)
- Relative reductions of 94% and 95% (both p<0.0001) in the number of T1- gadolinium (Gd)-enhancing lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively
- Relative reductions of 77% and 83% (both $p < 0.0001$) in the total number of new and/or enlarging T2 hyperintense lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively

In a Phase III global PPMS trial (Study WA25046), ocrelizumab 600 mg demonstrated statistically significant superiority compared with placebo on each of the following major efficacy endpoints (Montalban et al. 2015)

- A 24% relative risk reduction in 12-week CDP, the primary endpoint (HR = 0.76 [95% CI: 0.59, 0.98], $p = 0.0321$)
- A 25% relative risk reduction in 24-week CDP (HR = 0.75 [95% CI: 0.58, 0.98], $p = 0.0365$)
- Relative reduction of 29% in the progression rate of timed 25-foot walk from baseline to Week 120 ($p = 0.0404$)
- A decrease in the volume of T2 lesions by 3.4% over 120 weeks, compared with the placebo group in which the T2 lesion volume increased by 7.4% ($p < 0.0001$)
- Relative reduction of 17.5% in whole brain volume loss from Week 24 to Week 120 ($p = 0.0206$).

Clinical Safety

The safety data included are from five studies in MS: two Phase III studies in RMS (Studies WA21092 and WA21093), one Phase III study in PPMS (Study WA25046); one Phase II study in RRMS (Study WA21493) and one substudy (shorter infusion substudy) of the Phase IIIb study in early stage RRMS (Study MA30143).

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

In the two double-blind, double-dummy RMS Phase III studies (pooled data of Studies WA21092 and WA21093) during the 96-week controlled treatment period, the rates of treatment discontinuations for adverse events (AEs) were lower in patients treated with ocrelizumab 600 mg (3.5%) than in patients receiving IFNβ-1a (6.2%). The proportion of patients with AEs (83.3% in both groups) as well as the total number of AEs were similar in the ocrelizumab and the IFNβ -1a treatment groups over the 96-week treatment period. The proportion of patients reporting infections was higher in the ocrelizumab group compared with the IFNβ-1a group, (58.4% vs. 52.4%, respectively). In addition, there were more events of infection in the ocrelizumab group (1224 events) compared with the IFNβ -1a group (948 events) and these were primarily upper respiratory tract infections of Grade 1 or 2 intensity. The proportion of patients with serious adverse events (SAEs) was lower in the ocrelizumab treatment group than in the IFNβ-1a treatment group (6.9% in the ocrelizumab treatment group versus 8.7% in the IFNβ-1a treatment group). Overall, the proportion of patients with serious infections was lower in the ocrelizumab group (1.3%) than in the IFNβ-1a group (2.9%). Two serious infusion-related reactions (IRRs) were reported; one in the IFNβ -1a group (severe balance disorder and other symptoms; Grade 3) and one in the ocrelizumab group (life threatening bronchospasm; Grade 4). As expected, the proportion of patients experiencing IRRs were increased in the ocrelizumab group (34.3%) compared with the active control group (9.7%) who received dummy infusions. During the 96-week controlled treatment period, a total of 6 malignancies were reported, 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFNβ -1a treatment group and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group. Three deaths occurred in Studies WA21092 and WA21093; 2 patients (suicide and mechanical ileus) in the IFNβ -1a treatment group and 1 patient (suicide) in the ocrelizumab treatment group.

In the PPMS Phase III double blind placebo controlled Study WA25046, the proportion of patients with AEs leading to discontinuation from treatment was similar in ocrelizumab (4.1%) and placebo (3.3%) groups. The proportion of patients who experienced at least one AE was 90% in the placebo group compared with 95% in the ocrelizumab group. Taking into account that twice as many patients were randomized to ocrelizumab than placebo, the number of AEs experienced by patients with an AE was similar (1762 events in the placebo group and 3690 events in the ocrelizumab group). The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The proportion of patients with serious infections was similar in both groups: 5.9% in the placebo group compared with 6.2% in the ocrelizumab group. As expected, the proportion of patients who reported IRRs was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group. During the controlled treatment period, a total of 15 malignancies in 13 patients were reported: 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients

(0.8%) in the placebo group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large-cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group. The proportion of patients with SAEs (22.2% in the placebo group compared with 20.4% in the ocrelizumab group), was similar in both groups. There were 5 deaths during the controlled treatment period, one in the placebo group (road traffic accident) and 4 in the ocrelizumab group (pulmonary embolism, pneumonia, pancreatic carcinoma, pneumonia aspiration).

The primary analysis of the shorter infusion substudy of the main MA30143 study (a phase IIIb study in early stage RRMS) suggested that the frequency/severity of IRRs were comparable between the conventional ocrelizumab infusion (administered over ~3.5 hours) and the shorter ocrelizumab infusion (administered over ~2.0 hours); no new safety signals were detected. As of September 2019, 291 and 289 patients were randomized to the conventional and shorter infusion groups, respectively. Following the first randomized infusion, 67 patients (23.1%) in the conventional and 71 patients (24.6%) in the shorter infusion group experienced IRRs. The majority of IRRs were mild or moderate; >98% of all IRRs resolved without sequelae in both groups. No IRRs were life-threatening, serious, or fatal; one severe IRR occurred in both the conventional (laryngeal inflammation [second randomized dose]) and shorter infusion groups (fatigue [first randomized dose]). No IRR-related discontinuations occurred. During the first randomized dose, 14 (4.8%) and 25 (8.7%) patients in the conventional and shorter infusion groups had IRRs leading to infusion interruption/slowing, respectively (data on file).

All Exposure Population

The safety data from controlled periods of Studies WA21092 (Phase III, RMS), WA21093 (Phase III, RMS), WA25046 (Phase III, PPMS), and Study WA21493 (Phase II, RRMS) as well as BN29739, MA30005, MA30143, ML29966, MN30035, MN39158 and MN39159 are included up to a clinical cut-off date (CCOD) of January 2020. A total of 5,680 patients exposed to ocrelizumab, accounting for 18,218 patient years (PY), are included in this section (MS All Exposure Population).

The most common AEs were IRRs which were manageable using appropriate measures, and infections, mostly Grade 1 or Grade 2 in intensity. The overall rate of serious infections (SIs) remains low and stable. Urinary tract infection and pneumonia remained the SIs events reported with the highest rates per 100PY. The event rate per 100PY of SIs appears to increase numerically with fluctuation over time driven solely by the PPMS population subset. The majority of SIs were of Grade 3 intensity or below, resolved without sequelae, within ≤ 2 weeks and were not treatment limiting. Though malignancy remains a potential risk and needs to be further characterized, the incidence

rate of malignancy in ocrelizumab treated patients remained consistent with that of the general MS population.

For more detailed information on safety from clinical trials and post-marketing settings, please refer to the most recent version of the IB.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

It is widely understood that the clinical course of MS consists of two major phases; an early, focal inflammatory phase and a later, progressive, inflammatory-independent neurodegeneration phase (Leray et al. 2010). Focal damage manifests clinically mainly as relapses, whereas diffuse damage has been more closely associated with disability progression and cognitive decline (Ziemssen et al. 2015). Studies have shown, however, that neurodegeneration can in fact begin early in the disease course and can contribute to ongoing disease activity, but this may not always be clinically evident in the initial stages (Ziemssen et al. 2015). It is argued that once neurodegenerative features are clinically detectable, permanent damage has already accumulated making it difficult to improve outcomes (Freedman 2011). Furthermore, each relapse that patients with RRMS experience may be associated with accumulation of irreversible neurological damage and disability (Noyes and Weinstock-Guttman 2013). For example, in the natural history RRMS cohort study, patients were stratified according to number of relapses in the first 2 years, first inter-attack interval and number of relapses from year 3 to onset of progression. More relapses in the first 2 years were related to a higher probability to convert to SPMS (HR = 1.1; p = 0.003) and latency between disease onset and onset of progression was significantly longer in groups with 1 versus ≥3 relapses during the first 2 years (p = 0.014) (Scalfari et al. 2010). One of the early studies including patients with RRMS (Jacobs et al. 1996) early in the disease (Expanded Disability Status Scale [EDSS] at baseline 1.0 – 3.5) demonstrated that the IFNβ-1a treatment reduced the CDP significantly after two years compared to placebo. An eight-year follow-up of these patients (Rudick et al. 2005) could demonstrate that patients who received the initial IFNβ-1a treatment had a significant lower risk at reaching an EDSS of 6.0 compared to the initial placebo group. This demonstrated that the delay in start of DMT therapy did not allow to catch up on the progression of the disability on long term. Therefore, optimizing treatment early in MS may prevent the accumulation of irreversible neurological damage and reduce the risk of disease progression (Ziemssen et al. 2015).

The majority of the clinical trials of DMTs in MS target patients who are already progressed, for example the mean duration of disease is around six years for many clinical trials (Wiendl and Meuth. 2015). There is, however, evidence suggesting that early intervention might be effective in reducing the rate of relapses in patients with RRMS and in slowing the course of MS progression (Noyes and Weinstock-Guttman 2013).

A follow-up of the phase 3 clinical trial (n = 160) of IFNβ-1a vs. placebo in early RRMS patients described above, patients randomized to IFNβ-1a (n=79) were significantly less

likely to progress to an EDSS score of 4.0 or greater (44.3% vs 65.4%; P=.007) or 5.0 or greater (34.2% vs 54.3%; P=.01) than patients randomized to placebo (n=81) at the 8-year follow-up assessment (Rudick et al. 2010). Other long-term studies have also demonstrated a positive impact of early therapy in patients with RRMS. In a long-term follow-up of the pivotal PRISMS study (n=560), patients originally randomized to both the 22-µg and 44-µg doses of IFNβ-1a had sustained reductions in relapses and less disease progression compared with patients originally randomized to placebo. Although all patients received IFNβ-1a treatment by year 3 of the pivotal study (patients originally randomized to placebo were switched to either the 22- or 44-µg dose), the increased disability observed in patients for whom treatment was delayed was sustained (Kappos et al. 2006), suggesting that delaying treatment for as little as 2 years may result in irreversible consequences.

The Phase II study of ocrelizumab provided initial evidence that ocrelizumab could be effective at reducing MS disease activity following initial IFN-β therapy, and efficacy in reducing the disease activity as measured by T1 Gd enhancement already after 8 weeks was demonstrated. Moreover, two pivotal phase III trial in RRMS have shown that ocrelizumab is more efficacious in risk reduction of CDP than subcutaneous IFNβ-1a with a comparable safety profile. However, the study population in these two pivotal studies did not specifically include early RRMS patients.

Given the evidence on the potential long-term benefits of early treatment of RRMS with DMTs, and given the favorable risk: benefit profile of ocrelizumab to date, it will be valuable to characterize the clinical profile of ocrelizumab in early RRMS patients. As there is limited data on the effectiveness of ocrelizumab in this population, a dedicated prospective study to specifically evaluate the clinical profile is required and justified.

2. OBJECTIVES AND ENDPOINTS

The main study will evaluate the effectiveness and safety of ocrelizumab in patients who are in early stage of RRMS.

Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the effectiveness of ocrelizumab in early stage of RRMS	• Evaluate clinical measures related to disease progression over 4 years in patients in the early stage of their RRMS disease
Overview of the effectiveness measures:	
• Different effectiveness measures evaluated for ocrelizumab in early stage of RRMS	**Related to disability progression**: • Time to onset of CDP sustained for at least 24 weeks and 48 weeks

Objectives	Corresponding Endpoints
	• Proportion of patients who have confirmed disability improvement (CDI), CDP for at least 24 weeks and 48 weeks at year 1, 2 and 4 • Proportion of patients who have improved, stable or worsened disability compared with baseline measured by EDSS annually • Mean change from baseline in EDSS score over the course of the study **Other clinical measures and composite endpoints:** • Time to first protocol-defined event of disease activity • Time to first relapse • Annualized relapse rate • Proportion of patient relapse free by week 48, 96, 144 and 192 • Proportion of patients with no evidence of protocol-defined disease activity (NEDA) over week 96, week 144 and week 192 where disease activity is defined as at least one the following events: protocol-defined relapse; CDP based on increases in EDSS; a T1 Gd-enhanced lesion after Week 8; or a new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan. • Proportion of patients with no evidence of progression (NEP) defined as no progression sustained for at least 24 weeks on all of the following three components (CDP; 20% increase in timed 25 Foot Walk Test [T25FWT]; 20% increase in timed 9 hole peg test [9HPT]) between baseline and week 96/192 • Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD) defined as no progression on all of the three components of NEP (CDP, T25FWT, 9HPT), no new relapse and no enlarging or new T2 or T1 Gd-enhancing lesion between baseline and week 96/192 • Change from baseline of Multiple Sclerosis Functional Composite (MSFC) and its composites (T25FW, 9HP, and Paced Auditory Serial Addition Test [PASAT]) over time • Change from baseline in cognitive performance as measured by Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) performed annually **Related to MRI** • Total number of T1 Gd-enhancing lesions as detected by brain MRI over time • Total number of new and/or enlarging T2 lesion as detected by brain MRI over time • Change in total T1 hypointense lesion volume over time

Objectives	Corresponding Endpoints
	• Total number of fluid-attenuated inversion-recovery (FLAIR) late enhancing lesions as detected by brain MRI over time • Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time **Other measures related to MS disease:** • Time to treatment discontinuation/switch **Patient reported outcomes:** • Employment status (Work Productivity and Activity Impairment Questionnaire [WPAI]) • SymptoMScreen • Quality of life (Multiple Sclerosis Impact Scale [MSIS]-29)
Exploratory Objectives:	
• To further evaluate the effectiveness of ocrelizumab in early stage of RRMS	• Markers or predictors/indicators of disease progression (clinical and MRI markers) at week 24, week 48 and week 96 • Severity of relapses (hospitalization, use of corticosteroids, residual disability)
• To investigate the impact of ocrelizumab therapy on biomarkers associated *with* neurodegenerative mechanisms and/or other biomarkers in early stage RRMS	• Changes in levels of neurofilament light chain (NfL), levels of soluble neurodegeneration markers and/or other biomarkers in peripheral blood serum or plasma
• *To investigate the effect of ocrelizumab on antibody and T cell responses in patients administered an approved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine*	• *Analysis of immune response (SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses) to SARS-CoV-2 vaccine*
Safety Objective:	
• To evaluate the safety and tolerability of ocrelizumab in early stage of RRMS	• Rate and nature of adverse events • Changes in vital signs, physical and neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS CNS pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration)
Optional sub-studies in selected countries and at selected sites:	
T and B cells impact sub-study in France 288 weeks longitudinal, multi-center, sub-study (n=~50) Participating centers are restricted to French investigator centers with PBMC (peripheral blood mononuclear cell) technical and storage capacity.	• Impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients, indirect impact of ocrelizumab on B cell repopulation and relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab
Immune sub-study in Germany and other selected countries (n=~80)	• Frequencies of circulating immune cell subsets (B cells, T cells, NK cells, antigen presenting cells)

Objectives	Corresponding Endpoints
Ocrelizumab shorter infusion substudy (approximately 700 patients: of which approximately 550 additional patients and approximately 150 currently participating in the main study)	• Proportion of patients with IRRs occurring during or within 24 hours following the first infusion after randomization to the shorter infusion substudy

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following while on treatment with ocrelizumab:

- a protocol-defined relapse as defined in Section 4.5.5
- CDP based on increases in EDSS *(see Section 4.5.6)*
- a T1 Gd-enhanced lesion after Week 8
- a new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

The main study is a prospective, multicenter, open-label, single-arm effectiveness and safety study in patients with early stage RRMS. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks (± 14 days) for the remainder of the study duration.

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

The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 192 weeks (i.e. 24 weeks after the last dose of ocrelizumab, which will be administered at Week 168)
- A *safety* follow-up period of 48 weeks *after the last infusion of the study drug*, as explained below

Safety Follow-up Period: Patients who discontinue treatment early *for any reason and patients who complete the study treatment period and do not continue in a separate long-term extension (LTE) study,* will be followed up for 48 weeks after the last infusion of study drug. *When patients begin an alternative treatment for MS (see section 4.4.1 "Prohibited Therapy"), they will be discontinued from the study.*

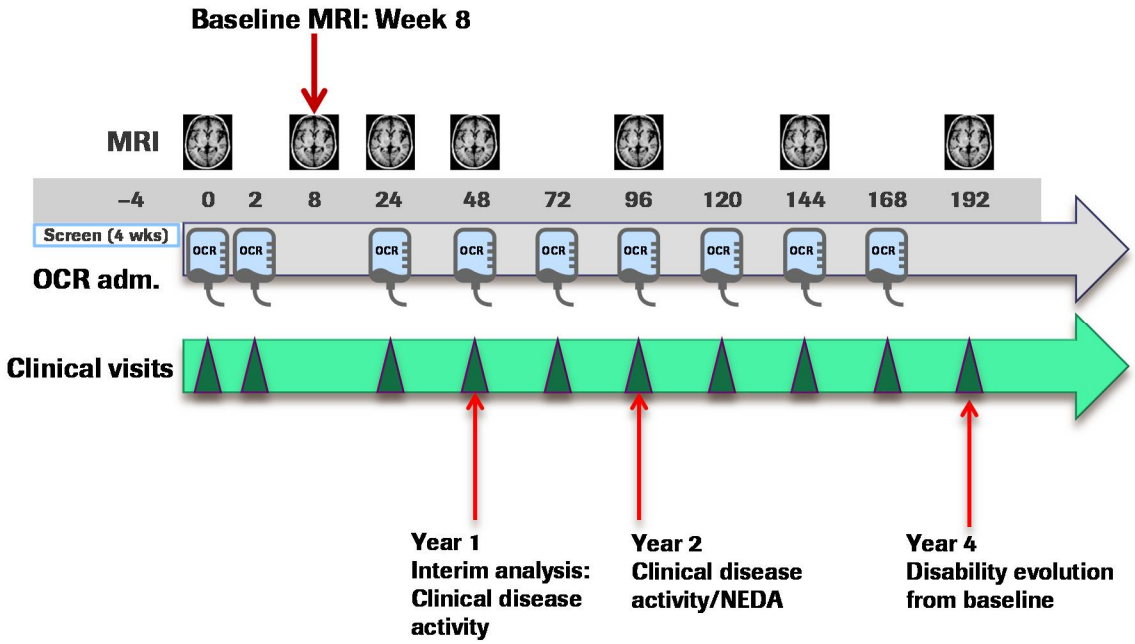
Patients who discontinue study treatment and switch to commercially marketed ocrelizumab, either after completion of the 192 weeks Treatment Period or after early discontinuation of the 192 weeks Treatment Period, will not enter the safety Follow-up Period.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits (starting after the site visit at 8 weeks) during the treatment period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.

3.1.1 Overview of Study Design

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

Figure 1 Overview of Study Procedures



MRI = magnetic resonance imaging; OCR = ocrelizumab; NEDA = no evidence of disease activity

3.1.2 Screening

After providing written informed consent, patients will enter a screening period (up to 4-weeks) to be evaluated for eligibility.

Re-screening of patients is allowed in this protocol.

3.1.3 Treatment Period

Eligible patients will be treated with an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks (±14 days) for the remainder of study duration.

Additional patients enrolled into the shorter infusion sub-study were randomized into 2 groups at week 24 visit. One group received 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks (±14 days) for the remainder of the study duration (as in the main study) and the other group received 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour) starting from week 24 for the remainder of the study duration. Please see Appendix 10 for further details. Patients already enrolled in the main study were offered to participate in the shorter infusion substudy and were randomized into the above 2 groups at the next main study visit if found eligible and after providing written informed consent. The protocol amendment version 8.0 marked the completion of the shorter infusion substudy and patients will continue under the main study protocol.

Based on the results of the primary analysis of the shorter infusion substudy, patients will be allowed to switch from the conventional ocrelizumab infusion (~3.5 hours) to the shorter ocrelizumab infusion (~2.0 hours) at any visit after the Week 24 visit based on the schedules of infusion as per the protocol, after providing written informed consent and in agreement with their treating physician, provided they have not experienced any previous serious IRRs with ocrelizumab treatment. While on the shorter infusion, the patients can switch back to the conventional infusion, in agreement with their treating physician. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

*All l*aboratory samples can be taken up to 2 weeks prior to the scheduled study visit. Local laboratory results for hematology, biochemistry and CD4 should be available prior to dosing as they are re-treatment criteria. Local laboratory results for CD8 and CD19 may be available later, as they do not need to be verified prior to re-treatment. Samples for NfL, anti-drug antibodies (ADA), and ocrelizumab concentration are collected and sent to the central laboratory for analysis. Please see Section 4.5.8 for further details

After the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24-week and 48-week CDP (CDP/CDI confirmation visit). For those patients presenting with an EDSS change at the end of the treatment period and who roll over to the LTE study (Study MN39158), the 24-week and 48-week CDP confirmation visits will occur during the LTE study (Study MN39158). For patients who discontinue the study (e.g., move onto commercial ocrelizumab, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.

Sub-studies will be conducted in selected countries according to local approvals and procedures. Please refer to Appendices 8, 9, and 10 for the sub-study protocols.

Criteria for Re-Treatment with Ocrelizumab

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

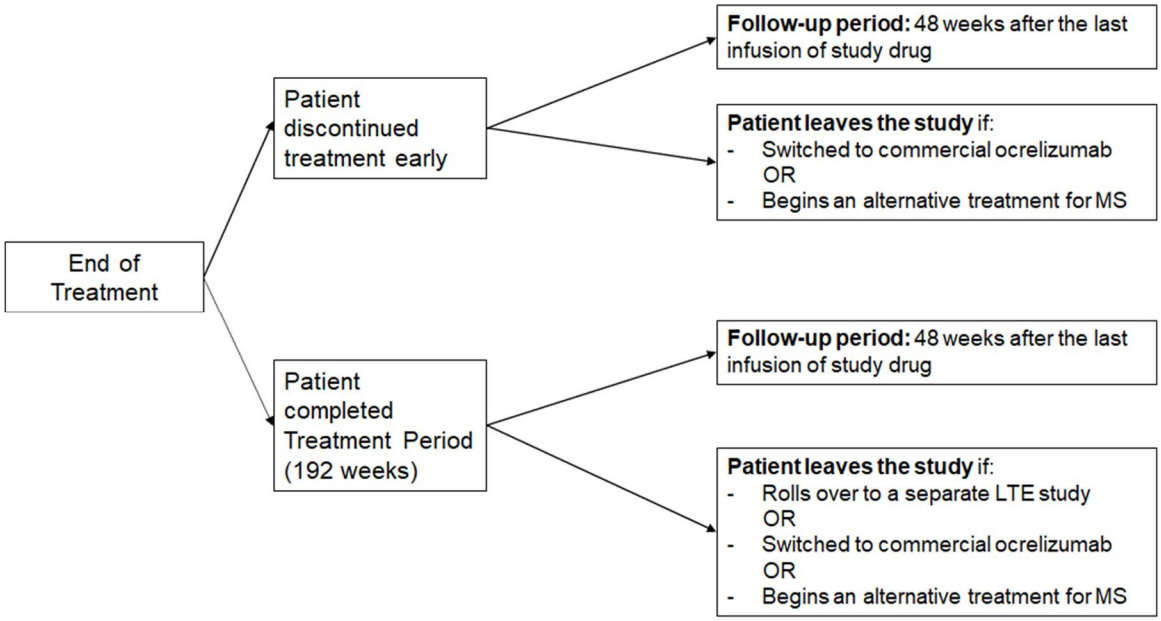
- Life threatening (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Current active infection other than a fungal nailbed infection. The re-treatment should be delayed until the active infection is treated and patient fully recovered
- CD4 cell count < 250/µL
- Absolute neutrophil count (ANC) $<1.0 \times 10^3$/µL
- Elevated aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT) ($>3 \times$ the upper limit of normal [ULN]) in combination with either an elevated total bilirubin ($>2 \times$ ULN) or clinical jaundice
- Hepatitis B screening tests prior to ocrelizumab administration
    - If total hepatitis B core antibody (HBcAb) was positive at screening, hepatitis B virus (HBV) deoxyribonucleic acid (DNA) measured by polymerase chain reaction (PCR) must be negative in order for a patient to be dosed with ocrelizumab. For patients with negative hepatitis B surface antigen (HBsAg) and positive total HBcAb, HBV DNA testing (by PCR) must be repeated every 24 weeks and evaluated prior to ocrelizumab administration. If it becomes positive, treatment with ocrelizumab must be discontinued and the patient should enter the safety follow-up.
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Ongoing pregnancy or breastfeeding (In case of unplanned pregnancy, treatment should be interrupted, however the patient will remain in the trial and will have the opportunity to re-start ocrelizumab treatment after birth and breastfeeding are over. The total duration of treatment period will be 192 weeks from the date of first dose of ocrelizumab, irrespective of how long the treatment was interrupted due to pregnancy. During pregnancy and breastfeeding, the patient will continue to come for the regular scheduled visits (whenever possible, adhering to the time of scheduled visits as per protocol) and will perform all assessments except MRI.

At the end of the study treatment the patients will be encouraged to be included in a separate LTE (MN39158) study, as applicable, to further evaluate the effectiveness and safety of *ocrelizumab treatment.* This LTE will also aim to evaluate the long-term outcome*s with ocrelizumab treatment over the extended period of time in patients with MS.*

Figure 2 Overview of End of Treatment Period *provides an overview of the end-of-treatment period. (Please see Section 3.1.4).*

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits (starting after the site visit at 8 weeks) during the treatment period to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.

Figure 2 Overview of End of Treatment Period



LTE = Long-term extension; MS = Multiple sclerosis

3.1.4 *Safety* Follow-up Period

Patients who discontinue treatment early *for any reason and patients who complete the 192 weeks Treatment Period and do not continue in a separate LTE study* will be followed up for 48 weeks after the last infusion of study drug. *When patients begin an alternative treatment for MS (see section 4.4.1 "Prohibited Therapy"), they will be discontinued from the study.*

Patients who discontinue study treatment and switch to commercially marketed ocrelizumab, either after completion of the 192 weeks Treatment Period or after early discontinuation of the 192 weeks Treatment Period, will not enter the *Safety* Follow-up Period.

A schedule of assessments for the *Safety* Follow-up Period is presented in Appendix 2.

During the *Safety* Follow-up Period, patients will be formally assessed at clinical visits every 24 weeks.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study through the end of the Safety Follow-Up Period, which is 48 weeks after the last infusion. Non-serious adverse events have to be reported until the end of Safety Follow-up Period.

For patients withdrawing from treatment early, every effort should be made to complete the *Safety* Follow-up Period and all related assessments.

3.1.5 Planned Total Sample Size

The main study was initially planned to enroll at least 600 patients. Please refer to the Section 6.1 for more details.

Approximately 550 additional patients were to be enrolled in the shorter infusion sub-study. They would also be enrolled in the main study (see Appendix 10 for more details).

Therefore, the main study would enroll a total of at least 1,100 patients. A total of 1,225 patients (678 in the main study and 547 in the shorter infusion substudy) were enrolled in the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the main study is defined as the last patient last visit *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*

The end of the study treatment period has been defined as the date on which the last patient receiving the full study treatment reached the 192-week visit. *After the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24-week and 48-week CDP (CDP/CDI confirmation visit). For those patients presenting with an EDSS change at the end of the treatment period and who roll over to the LTE study LIBERTO (Study MN39158), the 24-week and 48-week CDP confirmation visits will occur during the LTE study (Study MN39158). For patients who discontinue the study (e.g., move onto commercial ocrelizumab, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.*

The total length of the main study, from screening of the first patient to the end of the study depends on the recruitment rate and is expected to be approximately *356* weeks (~7 years). This includes an enrolment period of 116 weeks.

3.3 RATIONALE FOR STUDY DESIGN

The main study is a Phase IIIb, prospective, multicenter, open-label singe-arm study to assess the effectiveness and safety of ocrelizumab in patients in the early stage of RRMS.

As the efficacy and safety of ocrelizumab has already been demonstrated in pivotal double-blind, randomized controlled trials as described in Section 1.2, a single arm approach for this study, where the goal is to characterize the clinical profile of the drug in early patients, is considered to be appropriate. As the effect of existing standard of care treatments on the clinical course of early RRMS is already well established in the literature (Noyes and Weinstock-Guttman 2013; Rudick et al.2010), no direct comparators are required for this study. The main analyses will be in the form of descriptive statistics examining change from baseline to endpoint across the outcome parameters for the entire study sample, and for sub-groups of interest. A study duration of 4 years is considered to be sufficient to show a reliable and relevant effect of ocrelizumab on disability progression (EMA/CHMP/771815/2011, Rev. 2, 2015). Given the potentially long-term use of ocrelizumab in MS, this study of 4 years duration will provide additional safety data in a population with early stage of RRMS to be contextualized with the population studied in the pivotal phase III trials.

The effectiveness of ocrelizumab will be evaluated based on various clinical outcomes related to disease progression over 4 years.

One of the key outcome measures is time to onset of confirmed CDP sustained for at least 24 weeks and 48 weeks with CDP defined as 1-point or greater worsening in EDSS from baseline. An increase of 1 point on the EDSS above baseline, subsequently confirmed at repeat assessment either 3 or 6 months later (3 or 6 month confirmed progression) is the most commonly used measure in MS clinical trials (Gray and Butzkueven. 2008). In RRMS, the precise measurement of disability is complicated by the unpredictable occurrence of exacerbations with variable recovery. To ensure that worsening in EDSS score represents permanent physical disability rather than an exacerbation-related temporary fluctuation in neurological status, a worsening EDSS score has to be sustained for at least 6 months for a patient to be considered a treatment failure. Previous studies have shown that spontaneous recovery from sustained progression of 1.0 EDSS point of this duration is most unusual (Jacobs 1996). CDP is therefore a robust measure when performed over a 6-month interval, and reduction in the risk of 6-month CDP provides good evidence for the beneficial effects on disability of several high-efficacy treatments for RRMS (Wiendl et al. 2015).

EDSS is the most widely used and well-known scale to assess changes in disability in MS. Evaluation of change from baseline in EDSS score over the course of the study will provide an overall estimate of the dysfunction that was experienced by the patient during the study period.

Other key end-points such as MRI variables (for example, lesion count, lesion volume, and brain volume) are commonly used in clinical trials to assess treatment efficacy and disease progression (Lavery et al. 2014). Based upon the Phase II data, and to allow the real evaluation of the treatment effect, MRI activity will be evaluated starting from week 8 in this study. Time to onset of first relapse and proportion of patients who are relapse

free are also acceptable parameters to assess relapse-status in RRMS clinical trials (EMA/CHMP/771815/2011, Rev. 2, 2015).

It is recognized that the EDSS does not adequately assess upper limb function and cognitive impairment and the use of specific methods could be useful. In this context, quantitative neurological performance tests, for example MSFC may be used as secondary measurements of disability. The MSFC score combines a measure of lower limb function (T25FWT), upper limb function (9HPT) and cognitive function (PASAT) and is useful to detect disability progression in MS trials, as it is sensitive to change over time. The scores for each test are normally distributed, and are highly responsive to change over 2 years, thus producing much greater statistical power to detect change in the context of clinical trials (Gray and Butzkueven. 2008).

Prevention of disability progression as measured by the different elements: CDP but also upper limb function (9HP) and lower limb function (T25FW) are from early on important for the patient to allow optimal functioning. In RRMS, beside the disability, also clinical and subclinical elements of disease activity (relapses, T1 Gd+ and new/enlarging T2 lesions) remain of importance since these elements can contribute to the progression of the disability or the MS disease in general.

As the burden of cognitive impairment in MS is considerable, and is of crucial significance in employment outcomes and social disability (Gray and Butzkueven. 2008), the BICAMS, an international expert consensus recommended and validated battery of tests for mental processing speed and memory (Benedict et al., 2012) will be used as a secondary outcome measure to assess the changes from baseline in cognitive performances.

MS is a chronic, disabling condition having a significant impact on patients quality of life (QoL) and therefore MSIS-29, a clinically useful and scientifically-sound patient-based outcome measure of the impact of MS in clinical trials (Hobart et al. 2001) will be used as a key exploratory outcome measure to assess the physical and psychological impact of MS from the patient's perspective.

During the controlled treatment periods of the Ocrelizumab Phase III studies approximately 1% (12/1311) of ocrelizumab-treated patients tested positive for treatment-emergent ADAs. Some of the inclusion criteria are different in this study compared to the pivotal studies. Moreover, commercial material is introduced in the phase IIIb studies for which no immunogenicity data are available. Therefore, ADAs will also be assessed in this study for two years.

Rationale for measuring impact of ocrelizumab on response to SARS-CoV-2 vaccines

The results of the randomized, open-label Phase IIIb study (VELOCE), which assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines, indicate that patients with RMS who are peripherally B-cell depleted after treatment with ocrelizumab can

mount humoral responses, albeit attenuated, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The immune response of other components of the immune system (e.g., T cell response), known to confer immunological protection in addition to antibodies, were not evaluated.

Recently, vaccines against the SARS-CoV-2 virus have received authorizations for use from regulatory agencies. Vaccine efficacy data, and vaccine effectiveness from real world settings have shown that the available vaccines lead to a significant reduction in the number of COVID-19 infections and the number of severe cases that require hospitalization or result in fatal outcomes. Available data from the vaccine trials demonstrate that these vaccines can induce an antibody response as well as T cell responses. While not fully understood, accruing evidence suggests that both antibodies and T cell-mediated immunity have a protective role against future SARS-CoV-2 infection and severe clinical presentations. Currently, evidence on the SARS-CoV-2 vaccine response in persons taking immunomodulatory treatments is lacking, including in patients with MS treated with ocrelizumab.

Humoral immunity, including antibody titers, will be assessed by validated assays including the Elecsys SARS-CoV-2 Spike antibody test. SARS-CoV-2-specific T cell responses will be measured using a well-validated assay such as IFNg (interferon gamma) ELISpot (enzyme-linked immunospot). Immunophenotyping outcomes are to be assessed by flow cytometry. Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data.

Responses will be measured within a few weeks post-immunization and up to 18 months after the vaccination to evaluate the impact of ocrelizumab on the vaccine immune response over time.

3.3.1 Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in the main study is 600 mg. The first dose will be administered as two 300-mg IV infusions in 250 mL 0.9% sodium chloride each separated by 14 days in order to lower the amount of ocrelizumab administered upon first exposure. The remaining doses will be administered as single 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks (±14 days) to assess the tolerability of the intended administration regimen.

This dosing regimen is anticipated to be well-tolerated and is consistent with the dosing regimen used in Studies WA21092 and WA21093 in patients with RRMS.

3.3.2 Rationale for Patient Population

The main study will be conducted in treatment naïve early stage RRMS patients.

As the primary objective of the study is to evaluate the effectiveness of ocrelizumab in early stage of RRMS, length of disease duration from first symptom of ≤ 3 years, and a low EDSS score of 0.0 to 3.5 are the key entry criteria to ensure inclusion of this early population (Jacobs et al. 1996; Coles et al. 2008).

4. MATERIALS AND METHODS

4.1 PATIENTS

The main study was initially planned to enroll at least 600 patients with early stage RRMS who fulfil the eligibility criteria listed below. Approximately 550 additional patients were to be enrolled in the shorter infusion sub-study. They would also be enrolled in the main study (see Appendix 10 for more details). Therefore, the main study would enroll a total of at least 1,100 patients. A total of 1,225 patients (678 in the main study and 547 in the shorter infusion substudy) were enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18 – 55 years, inclusive
- Have a definite diagnosis of RRMS, as per the revised McDonald 2010 criteria (Polman et al. 2011)
- Have a length of disease duration, from first documented clinical attack consistent with MS disease of ≤ 3 years
- Within the last 12 months:

  One or more clinically reported relapse(s)

  OR

  One or more signs of MRI activity
- EDSS of 0.0 to 3.5 inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months or longer after the last dose of ocrelizumab, as applicable in the ocrelizumab package leaflet.

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

  The following are acceptable contraceptive methods (*failure rate >1%* as defined by the Clinical Trial Facilitation Group [CTFG] guidelines): *(1)* progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, *(2)* male or female condom with or without spermicide, *(3)* cap, diaphragm, or sponge with spermicide*, (4)* combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods).

  Birth control methods that are highly effective (i.e. failure rate <1% [CTFG]) may also be used but are not required, and include: (1) oral, intravaginal or transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or

implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomised partner; (7) sexual abstinence.

4.1.2 Exclusion Criteria

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

- SPMS or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia, weight>140 kg etc.)
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 (HTLV-1), herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease, sarcoidosis)
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Exclusions Related to General Health

- Pregnancy or lactation.
- Patients intending to become pregnant during the study or within 6 months after the last dose of the study drug.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study.
- History or currently active primary or secondary immunodeficiency.
- Lack of peripheral venous access.

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study.
- Congestive heart failure (New York Heart Association [NYHA] III or IV functional severity).
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks prior to screening or oral antibiotics 2 weeks prior to screening

  Note: Active infections must be treated and effectively controlled before possible inclusion in the study
- History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, progressive multifocal leukoencephalopathy [PML])
- History or known presence of recurrent or chronic infection (e.g., human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins.
- History of alcohol or drug abuse within 24 weeks prior to baseline.
- History or laboratory evidence of coagulation disorders.

<u>Exclusions Related to Medications</u>

- Received any prior approved DMT with a label for MS, for example, interferons, GA, natalizumab, alemtuzumab, daclizumab, fingolimod, teriflunomide and dimethylfumarate.
- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit.

  In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks.
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency).
- Contraindications to or intolerance of oral or IV corticosteroids, including methylprednisolone administered IV, according to the country label, including:

  a) Psychosis not yet controlled by a treatment

  b) Hypersensitivity to any of the constituents.
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).

- Systemic corticosteroid therapy within 4 weeks prior to screening.
- Any previous treatment with immunosuppressants/ immunomodulators/ antineoplastic therapies (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, cladribine, mitoxantrone, laquinimod, total body irradiation, or bone marrow transplantation).
- Treatment with IV Ig within 12 weeks prior to baseline.
- Treatment with investigational DMT
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- Treatment with fampridine/dalfamipridine (Fampyra®)/Ampyra®) unless on stable dose for ≥ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period

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]).
- Lymphocyte count below LLN
- CD4 count<250/µL.
- AST/ SGOT or ALT /SGPT≥ 3.0 × ULN
- Serum creatinine >1.4 mg/dL (> 124 µmol/L) for women or > 1.6 mg/dL (> 141µmol/L) for men
- Hemoglobin < 8.5 g/dL (< 5.15 mmol/L)
- Platelet count <100,000/µL (<100 × 10^9/L)
- Absolute neutrophil count <1.0 × 10^3/µL.

*Re-testing before baseline: 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.

Please note: based on local Ethics Committees (EC) or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 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 United States Pharmacopeia (USP), glass vial fitted with a 20-mm, fluoro-resin, laminated stopper and an aluminum seal with a flip-off plastic cap. The vial contains 300 mg ocrelizumab. No preservative is used as each vial is designed for single use, thus the vials should be handled aseptically.

The ocrelizumab drug product in vials should be stored at 2-8 degrees Celsius and protected from light, should not be frozen and not be shaken.

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

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

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2 – 8°C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, the total storage time of the infusion solution prior to administration should not exceed 24 hours at 2 to 8°C and 8 hours at room temperature for a total of 32 hours. In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab IB and Drug Preparation Guidelines.

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

The first dose of ocrelizumab will be administered as two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent doses (i.e., every 24 weeks ±14 days) for a maximum of 8 doses.

It is anticipated that the patient will need to stay at the hospital or clinic for the infusion visits. Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300 mg dose and for the 600 mg dose, it should be given over approximately 215 minutes (3.5 hours) for the conventional infusion and approximately 120 minutes (2.0 hours) for the shorter infusion. To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg intravenous methylprednisolone, or equivalent, administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion and antihistamine, via oral, intramuscular or IV route to be completed approximately 30-60 minutes and not less than 25 minutes prior to each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered). The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered. Additional premedication is recommended, see Section 4.3.3.

Additional patients enrolled into the shorter infusion substudy and randomized to the shorter infusion group received 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour) starting from week 24 for the remainder of the study duration. The patients received the same premedications as in the main study. Please see Appendix 10 for the details on infusion rate and time for the shorter infusion of ocrelizumab. The protocol amendment version 8.0 marked the completion of the shorter infusion substudy and patients will continue under the main study protocol.

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

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

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

See the Ocrelizumab IB and Drug Preparation Guidelines for detailed instructions on drug preparation, storage, and administration.

An overview of the ocrelizumab dosing is presented in Table 2 and the infusion rates for the conventional and the shorter infusions in Table 3.

Table 2 Overview of Ocrelizumab Dosing

Group	1st Dose[a,c] (Weeks 1 – 24)		2nd Dose[b,c] (Weeks 24 – 48 ± 14 days)	3rd Dose[b,c] (Weeks 48 – 72 ± 14 days)	4th Dose[b,c] (Weeks 72 – 96 ± 14 days)	5th Dose[b,c] (Weeks 96 – 120 ± 14 days)	6th Dose[b,c] (Weeks 120 – 144 ± 14 days)	7th Dose[b,c] (Weeks 144 – 168 ± 14 days)	8th Dose[b,c] (Weeks 168 – 192 ± 14 days)
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion	Week 96 Infusion	Week 120 Infusion	Week 144 Infusion	Week 168 Infusion
Ocrelizumab	300 mg IV in 250 mL 0.9% sodium chloride	300 mg IV in 250 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride

IV = intravenous.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for infusion-related reactions. Each dose has a duration of 24 weeks. The open-label treatment period consists of 192 weeks of treatment; patients will receive a maximum of 8 doses.

[a] The first dosing will consist of two IV infusions separated by 14 days (i.e., Days 1 and 15).

[b] Beginning with the second dose, a single infusion of ocrelizumab will be administered.

[c] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Table 3 Ocrelizumab infusion rates for Conventional and Shorter Infusions in absence of IRRs

Time (min)	Shorter infusion			Conventional infusion		
	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
0-15	100	30	30	40	23.18	23.18
16-30	200	60	90			
31-60	250	150	240	85	49.27	72.45
61-90	300	180	420	130	75.36	147.81
91-120	300	180	600	169	98.05	245.86
121 – 215	/	/	/	200	354.14	600

IRR = infusion-related reaction

Note: Patients will be allowed to switch from the conventional ocrelizumab infusion (~3.5 hours) to the shorter ocrelizumab infusion (~2.0 hours) at any visit after the Week 24 visit, based on the schedules of infusion as per the protocol, after providing written informed consent and in agreement with their treating physician, provided they have not experienced any previous serious IRRs with ocrelizumab treatment. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.

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

4.3.3 Prophylactic Treatment

The following premedications must be administered prior to each infusion of ocrelizumab to reduce the frequency and severity of IRRs:

- 100 mg intravenous methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion
- Antihistamine, via oral, intramuscular or IV route to be completed approximately 30-60 minutes and not less than 25 minutes prior to each ocrelizumab infusion (the antihistamine should be the first premedication to be administered)
- The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered

Any overdose or incorrect administration of methylprednisolone and antihistaminic drug should be noted on the Pre-Infusion Prophylactic Treatment eCRF. Adverse events associated with an overdose or incorrect administration of methylprednisolone and antihistaminic drug should be recorded on the Adverse Event eCRF.

Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

4.3.4 Investigational Medicinal Product Handling and Accountability

The IMP required for completion of the main study (ocrelizumab) will be provided by the Sponsor where required by local health authority regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for

maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMP supplied by the Sponsor, using the interactive voice/Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit*, either by time monitoring (shipment arrival date and time) or temperature monitoring,* for IMP received and that any discrepancies have been reported and resolved before use of the IMP. All IMP must be stored in a secure, environmentally-controlled and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMP, and only authorized staff may supply or administer IMP.

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

Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Dose Preparation Guidelines and/or the ocrelizumab IB for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Ocrelizumab

Patients may be eligible to receive ocrelizumab as part of an extension study (MN39158) to evaluate long-term effectiveness and safety, as described in Section 3.1.3.

The Sponsor will offer continued access to Roche IMP (ocrelizumab) 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 Roche IMP (ocrelizumab) 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 Roche IMP 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 Roche IMP (ocrelizumab) after completing the study if any of the following conditions are met:

- The Roche IMP 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 the IMP or data suggest that the IMP is not effective for RMS and PPMS
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for RMS and PPMS
- Provision of the Roche IMP 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 Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment within 6 weeks prior to the screening visit to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Prohibited Therapy

No formal drug-drug interaction studies have been conducted with ocrelizumab, as no drug-drug interactions are expected via the Cytochromes P450, other metabolizing enzymes or transporters.

Ocrelizumab is a monotherapy and has not been studied in combination with other DMTs. As with other immunomodulatory therapies, exercise caution when initiating ocrelizumab after an immunosuppressive therapy, and when initiating another therapy after ocrelizumab, taking into consideration the potential for overlapping pharmacodynamic effects.

Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers should NOT be administered while patient is B-cell depleted.

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

See the Ocrelizumab IB for a more detailed safety profile. In addition, the Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the main study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria and none of the exclusion criteria before enrolment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Patients' demographics (age, gender, self-reported race, and educational level), and neurological examination will be collected. Medical History will include clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 6 weeks prior to the screening visit:

MS disease history:
First MS symptom: date, symptoms, severity, MRI.
Diagnosis of MS:
Date, disease status, (EDSS, relapses, MRI) and, when available, criteria on which the diagnosis is based.
Baseline disease status:
EDSS, Number of relapses in the previous year, MRI lesions

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. The following assessments will also be conducted: neurological examination (see Section 4.5.5), relapse description, EDSS (see Section 4.5.6), and MRI (see Section 4.5.7). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF. Height and weight will be measured at screening only. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

4.5.4 Vital Signs

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

Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion, then every 15 minutes (±5 minutes) for the first hour, followed by every 30 minutes (±10 minutes) until 1 hour after the end of the infusion. Vital signs will be reported in the eCRF only in case of an IRR.

Vital sign measurements will be performed as outlined in the schedule of assessments (see Appendix 1). Record abnormalities observed before enrolment on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF (as presented in Section 5.3.5.6).

4.5.5 Neurological Examinations

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

A protocol-defined MS relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

- Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)
- Symptoms should be preceded by neurological stability for at least 30 days
- Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
  - ≥0.5 points on EDSS scale
  - or ≥2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
  - or ≥1 point on two or more of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual

Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse (Please note: Sexual dysfunction and fatigue need not be scored).

All patients with new neurological symptoms suggestive of a relapse should have an EDSS/FSS assessment performed as soon as possible, ideally within 7 days of the

onset of symptoms. EDSS/FSS data is needed to allow the sponsor to confirm whether the reported clinical relapse meets the criteria for a protocol-defined relapse.

Please note: All MS relapses (i.e., regardless of whether they may meet criteria for a protocol-defined relapse which will be adjudicated by the Sponsor based on the above criteria) will be recorded on a pre-specified eCRF “MS relapse” form. MS relapses should not be reported as an Adverse Event, unless they are serious.

As infection is a potentially serious complication of B cell-depleting therapy, investigators will also screen patients for signs and symptoms of any CNS infections and specifically PML by evaluating 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). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor. Please refer to Appendix 5 for guidance for diagnosis of PML.

Cognitive status: The cognitive status of the patient will be evaluated at baseline, and further yearly for the full duration of the trial with the use of BICAMS components.

4.5.6 Assessment of Disability

Disability in MS will be measured by the EDSS and MSFC. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral rated and scored as FSS. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score *(i.e., ambulation score 0 to 12). When determining the EDSS step, the Visual and the Bowel and Bladder FSS will be converted to a lower score as per the Neurostatus instructions. The original unconverted score should be recorded in the respective eCRF page.* The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see Appendix 3).

Disability progression has been defined as an increase of ≥ 1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. For patients with an EDSS of 0, progression is defined as a change >=1.5 points Disability progression is considered confirmed when the increase in the EDSS is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of neurological worsening.

CDI is defined as an improvement of 1 point on the EDSS score confirmed at a regular scheduled visit at least 24 weeks after the initial documentation of neurological worsening (measured only patients with a baseline EDSS of ≥2.0).

Stable disability is defined as a difference in EDSS score of no greater than ± 0.5 at the end of each year compared with baseline scores, worsened disability as an increase in EDSS score of > 0.5 at the end of each year compared with baseline, and improved disability as a reduction in EDSS score of > 0.5 at the end of each year compared with baseline.

MSFC is a score combining a measure of lower limb function (T25FWT), upper limb function (9HPT) and cognitive function (PASAT) used to detect disability progression in MS trials.

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions and potentially other pathophysiology, such as inflammation and neurodegeneration. Brain MRI scans will be obtained at study visits as shown in the Schedule of Assessments (see Appendix 1).

MRI scans will be read and assessed by a centralized reading center for effectiveness endpoints. As soon as the scan is received by the central MRI reading center, it will be evaluated for quality, completeness and adherence to the protocol including effectiveness endpoints. Confirmation of acceptable MRI quality or a description of the quality problems, if detected, will be communicated to the site. If the MRI scan is incomplete or incorrectly performed, the study center and the patient might be asked to repeat it. After completion of the quality check, all scans will be analyzed according to the MRI protocol.

Investigators must comply with local country regulations for MRI repetition. The final decision for the repetition of the MRI scans lies with the Investigator.

Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI scanners are described in a separate MRI technical manual.

Assessments will include T1-weighted scans before and after injection of gadolinium contrast, and may also include, but may not be limited to: FLAIR, proton density-weighted, and T2-weighted scans. The MRI activity will be based upon the MRI scan taken on week 8 when the drug has reached its anti-inflammatory activity.

The total brain volume and the different white and grey matter structures will be measured over the full duration of the study and follow-up period.

The brain MRI scan should be obtained within 14 days prior to the next ocrelizumab infusion and it should be reviewed by the local/treating investigator to exclude non-MS

pathology, including PML before the next infusion is administered. The MRI should be approved by the Medical Image Analysis Centre for efficacy evaluation before dosing with ocrelizumab.

If a patient receives corticosteroid for the treatment of a MS relapse, every effort should be made to obtain the scan prior to the first steroid dose, if the pre-steroid scan is within 1 week of the scheduled visit. In patients already receiving corticosteroids for an MS relapse, there should be an **interval of at least 3 weeks** between the last dose of corticosteroid and the scan, to allow normalization of the blood brain barrier.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples can be taken up to 2 weeks prior to the scheduled study visit. Local laboratory results for hematology, biochemistry and CD4 should be available prior to dosing as they are re-treatment criteria. Local laboratory results for CD8 and CD19 may be available later, as they do not need to be verified prior to re-treatment. Samples for NfL, ADA, and ocrelizumab concentration are collected and sent to the central laboratory for analysis. Please see details below.

Pre-infusion laboratory samples should be drawn so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

Routine laboratory assessments (performed in local laboratory) will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, percent and absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- Serum chemistries (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, creatinine, random glucose, potassium, sodium)
- Urine dipstick at site
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. A urine pregnancy test should be performed prior to methylprednisolone infusion in subsequent doses. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. The follicle-stimulating hormone (FSH) test is only applicable to confirm postmenopausal status in female patients.
- Viral serology and detection:
  - Hepatitis B (HBsAg and HBcAb confirmed, if positive, by positive viral DNA PCR)
  - For enrolled patients with negative HBsAg and positive total HBcAb, Hepatitis B virus (HBV) DNA (by PCR) must be repeated every 24 weeks
- Lymphocytes subtypes
  - Whole-blood samples will be collected to determine the duration of B-cell depletion and recovery ($CD19^+$) and T-cell counts ($CD4^+$, $CD8^+$)

Additional laboratory samples will be collected:

- Serum samples will be collected for determination of ocrelizumab concentrations and antibodies against ocrelizumab (ADA) for 2 years of treatment for each patient. Since ocrelizumab concentrations can affect the ADA assay, the concentration of ocrelizumab will be measured as well at all time points with ADA assessment to enable interpretation of the results. For details please refer to Schedule of Assessments (see Appendix 1). Sample should be collected before the methylprednisolone infusion. Following 2 years, samples should only be collected in any event of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction as close as possible to the event and then at 4- and 16-weeks post-dose.
- A serum sample will be collected before the methylprednisolone infusion *(if obtained on the days of ocrelizumab infusion),* and analysis may include, but will not be limited to NfL. This sample description covers retrospectively the serum collected for immunoglobulins *up to protocol* version *5.0.*

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

Per local Institutional Review Board (IRB)/EC requirements, additional testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HAM, AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

4.5.9 Patient-Reported Outcomes

PRO data will be elicited from patients in the main study to better characterize patient quality of life.

The MSIS-29 version 2 is the second version of 29-item questionnaire designed to measure the physical and psychological impact of MS from the patient's perspective (Hobart et al. 2001). Each question is scored on the scale of 1-4. The physical (20 items) and psychological (9 items) scales are scored separately. Scores are transformed into a 0-100 scale with higher scores indicating a greater degree of disability or impact of MS on the daily life of the patient.

The SymptoMScreen is a composite score based upon a battery of seven-point Likert scales for 11 distinct domains commonly affected by MS: mobility, dexterity, vision, fatigue, cognition, bladder function, sensation, spasticity, body pain, depression and anxiety. Total score (0-66) and subscale scores are assessed over the study duration (Green et al. 2015). Higher scores indicate greater severity of symptoms.

The Employment Status WPAI is a questionnaire that assesses working status and the impact of MS on absenteeism, presentism and the ability to perform regular activities.

Please refer to Appendix 6 for a sample copy of the PROs.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigator site prior to the completion of other study assessments and the administration of study drug. Patients must complete these measures prior to the patient having any tests and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site. The recommended order of administration is first the SymptoMScreen, followed by MSIS-29 and finally WPAI. PRO assessments will be performed as outlined in the schedule of assessments (see Appendix 1).

4.5.10 BICAMS

The BICAMS battery includes the following tests of mental processing speed and memory:

- Symbol Digit Modalities Test (SDMT)
- California Verbal Learning Test 2 (CVLT-II)
- Brief Visuospatial Memory Test Revised (BVMT-R)

Please note that the BICAMS should be administered only after the patient has completed all the PRO assessments. The recommended order of administration is first the SDMT, followed by the CVLT-II and then the BVMT-R. The BICAMS will be scored centrally by a global reader and the results will be provided to the sites to be recorded in the eCRF.

If the CVLT-II is not available in the subject's official language; patients will not be participating in this portion of the BICAMS test. The other two BICAMS test: Symbol Digit Modalities Test (SDMT) and Brief Visuospatial Memory Test Revised (BVMT-R) will still be completed by these patients.

4.5.11 Telephone Interviews

The telephone interview will be conducted by site personnel familiar with the patient(s) every 8 weeks (±3 days) between the study visits (starting after the site visit at 8 weeks) during the treatment period. The purpose of this semi-structured interview is to identify new or worsening neurological symptoms that warrant an unscheduled visit and collect information on possible events of infections. The site will record in the eCRF the telephone interview as "Done" or "Not Done" and documentation of the interview will be maintained in the patient's study file. Please refer to Appendix 4 for detailed information on the telephone interview questions.

4.5.12 Patient Diary (optional)

In the main study, the patient visits will occur every 24 weeks and site staff will conduct a telephone interview every 8 weeks in between the visits at site. Due to this visit frequency, patient diaries have been proposed as an optional tool to collect and

document adverse events and concomitant medication during the periods between visits, which would be transferred in eCRF at the next patient visit. The decision to use the patient diary is left to the discretion of each investigator. The investigator must ensure that required IRB/EC approval was obtained before implementing the patient diary at his/her site. See the guidance document to investigators for use of patient diary for additional details.

4.5.13 *Analysis of immune responses following SARS-CoV-2 vaccination (Optional Procedure)*

This optional procedure is applicable to only selected sites that allow the expedited processing of blood samples to central laboratories that are confirmed processing centers for this sample, as identified by study sponsor feasibility assessment. The Informed Consent Form will contain a separate section that addresses this optional procedure. A separate, specific signature will be required to document patient's agreement to undergo the described optional procedure.

For patients participating in the T and B cells impact substudy (Appendix 8) and the immune substudy (Appendix 9), blood collection for this optional procedure should not be performed at the visits with scheduled blood collection for the substudy assessments.

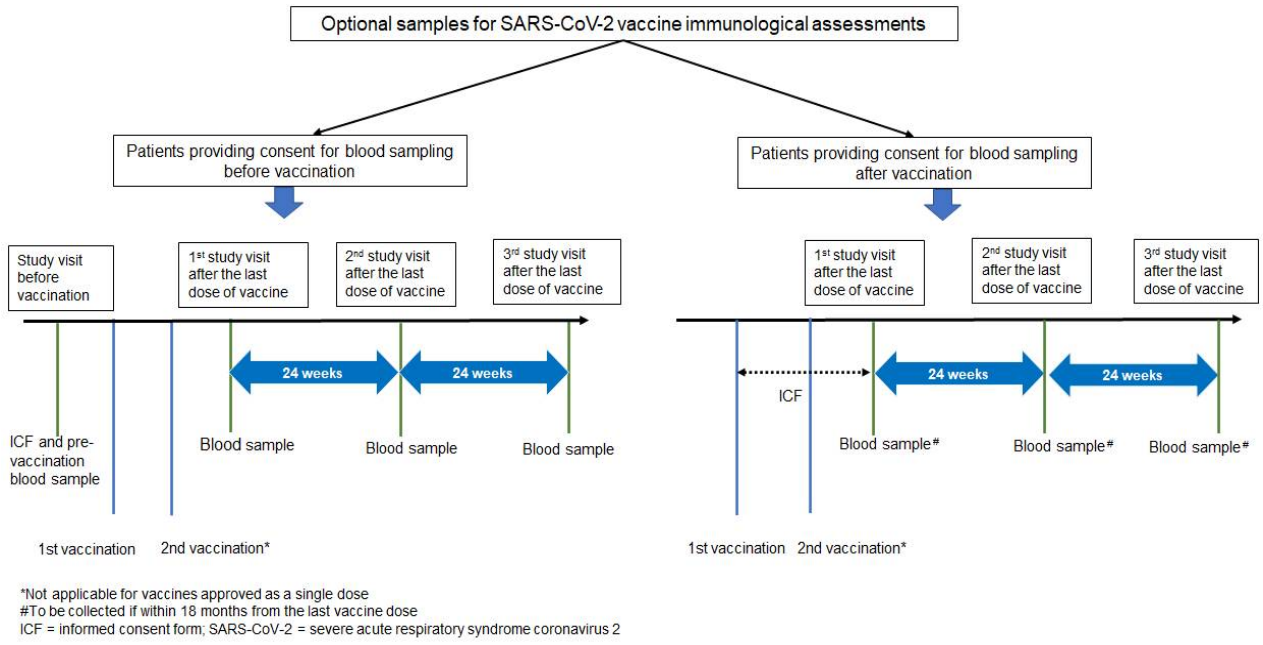
Samples for SARS-CoV-2 vaccine immunological assessments

- *Patients who receive the SARS-CoV-2 vaccine and who consent to provide the blood samples before the vaccination has occurred: the analyses of anti-SARS-CoV-2 antibody titers and T cell responses will be performed at maximum four time points: (1) at the study visit when the patient signs an optional informed consent form, prior to the administration of the vaccine, (2) at the next consecutive study visit(s) to a maximum of three visits following the last dose of vaccine. Please see Figure 3 for details.*
- *Patients who receive the SARS-CoV-2 vaccine and who consent to provide the blood samples after the vaccination has occurred: the analyses of anti-SARS-CoV-2 antibody titers and T cell responses will be performed at the next consecutive study visit(s) to a maximum of three visits after patient provided consent and following the last dose of the vaccine. Please see Figure 3 for details.*
- *A serum sample will be collected to evaluate the humoral immunity, including antibody titers. A whole blood sample will be collected and then processed centrally to allow for isolation of PBMCs and to measure SARS-CoV-2-specific T cell responses. Samples collected on the day of the ocrelizumab infusion must be collected prior to the IV methylprednisolone administration.*
- *When available, previously collected serum samples and whole blood/PBMC samples may be used to measure SARS-CoV-2 antibodies and T cell responses prior to the vaccination, in consenting patients.*
- *In patients who complete the parent study (ENSEMBLE) and who roll over to the LTE study LIBERTO (study MN39158), the sample collection can be carried over and performed according to the LIBERTO study schedule of visits. Patients will need to provide new consent to the optional procedure in the LIBERTO study.*

- *The study sponsor will terminate the collection of blood samples for this optional research when it is considered that enough interpretable data has been collected.*

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

Figure 3 Overview of Sample Collection for SARS-CoV-2 Vaccine Immunological Assessments for Optional Procedure



ICF = Informed consent form; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

4.6 OPTIONAL SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

4.6.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The whole blood sample for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression

- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.6.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.6.2) will not be applicable at that site.

4.6.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to Ocrelizumab, MS or related diseases:

- Blood sample collected at baseline for DNA (if the sample is not collected at baseline, it can be collected at any of the subsequent visits)
- Remaining blood, serum, plasma, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) from other samples collected in the study.

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

4.6.4 Confidentiality

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

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

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

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

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

4.6.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent*/Withdrawal* eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.6.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's

wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of *Informed Consent* withdrawal on the RBR Research Sample Withdrawal of Informed Consent/*Withdrawal* eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MA30143 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MA30143.

4.6.7 Monitoring and Oversight

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

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

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

- Pregnancy: patients becoming pregnant by chance during the study will be withheld from ocrelizumab treatment, but will remain in trial and will have the opportunity to re-start ocrelizumab treatment after the pregnancy/breastfeeding are over. During pregnancy and breastfeeding, these patients will continue to come for the regular scheduled visits (whenever possible, adhering to the time of scheduled visits as per protocol) and will perform all assessments except MRI. The total duration of treatment period will be 192 weeks from the date of first dose of ocrelizumab, irrespective of how long the treatment was interrupted due to pregnancy.
- Patients who plan to become pregnant during the study will be withheld from ocrelizumab treatment and will follow the recommendations for contraception period after the last infusion with ocrelizumab for at least 6 months or longer in accordance with locally applicable ocrelizumab package leaflet. Upon discontinuation of study treatment, these patients will enter the safety follow-up period but will not restart the study treatment.
- Life-threatening (NCI CTCAE Grade 4) IRR or serious hypersensitivity reaction
- New onset or reactivation of hepatitis B infection
- PML
- Any other serious adverse event, including laboratory values abnormalities, that present an unfavorable benefit-risk of treatment with ocrelizumab as deemed by the investigator.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patient discontinuing the study treatment prematurely will be further monitored in a safety follow-up (see Section 3.1.4).

Patients who discontinue study treatment prematurely will not be replaced.

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment.

4.7.2 Patient Discontinuation from Study

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Patient non-compliance, defined as failure to follow dosing instructions or to complete study visits

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.7.3 Study Discontinuation

The Sponsor has the right to terminate the main 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 enrolment is unsatisfactory.

Whenever needed, the investigator should reassess and discuss with the patient the benefits and risks of continuing with ocrelizumab treatment, and should, together with the patient, explore also alternative treatment options.

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

4.7.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab has been recently approved for the treatment of adult patients with relapsing or primary progressive forms of MS in several countries and regions including Australia/New-Zealand, Europe, Middle East, South America and the USA and for the treatment of adult patients in relapsing form of MS in Canada. Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the clinical program. Patient safety during the ocrelizumab program is ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in the main study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and standard laboratory measurements. Adverse events will be graded according to the National Cancer Institute (NCI) CTCAE $v5$.0.

Administration of ocrelizumab will be performed in a hospital, clinic environment or doctor's office/practice under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. All adverse events and serious adverse events will be recorded during the study and at 24 and 48 weeks (or until B-cell repletion) after the last dose of ocrelizumab as provided through this study. Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE $v5$.0. Safety assessments will be conducted per the schedule of assessments in Appendix 1.

The potential safety issues anticipated in the main study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

5.1.1 Risks associated with corticosteroids

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

5.1.2 Risks associated with antihistamines

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

5.1.3 Risks Associated with Ocrelizumab

5.1.3.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions

All CD20+ depleting agents administered via the intravenous route, including ocrelizumab have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab 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 the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but are 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.

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

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

Further details on prevention and management of infusion-related reactions are described in Section 5.1.4 and in the current IB.

Infections

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

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

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

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

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

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

For PML see “Potential risks” below.

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

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

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

Delayed return of peripheral B cells
Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients, indicates that the median time to repletion (returned to baseline/LLN whichever occurred first) of B cells was 72 weeks (range 27 − 175 weeks).

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, varicella were generally similar to the proportions at baseline.

The results of the randomized, open-label phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the IB.

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. For seasonal influenza vaccines it is still recommended to vaccinate patients on ocrelizumab. Vaccination with live-attenuated or live vaccines is not allowed during treatment and until B-cells have returned to normal levels.

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

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

5.1.3.2 Potential Risks

Progressive multifocal leukoencephalopathy (PML)
PML has been reported in patients receiving ocrelizumab but only in patients where other contributory factors were present, such as prior immunosuppressive treatment (for

example, natalizumab or fingolimod). Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for John Cunningham virus (JCV) DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Please refer to Appendix 5 for guidance for diagnosis of PML. Please see the IB for more details.

Hypersensitivity reactions

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

Malignancies including Breast Cancer

Patients should follow standard breast cancer screening guidelines.

Please see the IB for more details.

Neutropenia

In the controlled treatment period, decreased neutrophils were observed in 12 and 15% of MS patients treated with ocrelizumab, in PPMS and RMS respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. Based on additional patient exposure an association between neutropenia and serious infections with ocrelizumab treatment was not observed.

Additional information can be found in the current IB.

5.1.4 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 4. Additional guidelines are provided in the subsections below.

Table 4 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	• If the event that a patient experiences is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event. • This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.
Severe IRR (or complex of flushing, fever, and throat pain)	• If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. • The infusion should be re-started only after all symptoms have resolved. • The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.
Life-threatening or disabling IRR (e.g., anaphylaxis)	• Immediately stop ocrelizumab if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. • The patient should receive appropriate treatment. • Permanently discontinue ocrelizumab in these patients.

hr = hour; IRR = infusion-related reaction

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.1.4.

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); see Section 5.3.5.9 and Section 5.3.5.10 for more information

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

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

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

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

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

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

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

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5 and Section 5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 48 weeks after the last dose of study drug. Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. 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 (*v5*.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for infusion related reactions and adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for IRRs and Other Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (*v5*.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

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

Table 6 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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

recorded separately on the dedicated Infusion-Related Reaction eCRF. Please consider reporting a local IRR for any symptoms affecting only 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

For all adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). 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 time points. 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. Details regarding any increases in severity will be captured on the Adverse Event Intensity or Grade Changes 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 time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. 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 solely to progression of RRMS, "RRMS progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Relapsing Remitting Multiple Sclerosis

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of MS on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of multiple sclerosis). Events that are clearly consistent with the expected pattern of progression of the underlying disease, or other MS related symptoms, should not be recorded as adverse events. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- *Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones, and diagnostic testing. Such events should still be recorded as medical procedures in the ''Surgeries and Procedures'' eCRF.*
- *Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with i.v. methylprednisolone (or with another equivalent corticosteroid)*
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- 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 circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfils 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).

For ocrelizumab, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with ocrelizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

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

Adverse events associated with an overdose of ocrelizumab in previous clinical studies include IRRs and infection.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

Please note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Due to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, 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 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Emergency Medical Contact: [redacted] (Primary)

Mobile Telephone No.: [redacted]

Emergency Medical Contact: [redacted] (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, 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 paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 48 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system

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

Instructions for reporting serious adverse events that occur after the end of the adverse event reporting period 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. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator must withhold study drug for the duration of 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. Information about child heath up to 1 year should be collected on the infant health questionnaire (see Appendix 7).

Pregnancy: patients becoming pregnant by chance during the study will be withheld from ocrelizumab treatment but will remain in trial (patients will come at the clinic for the scheduled visits [wherever possible, adhering to the time of scheduled visits as per protocol] and will perform all assessments except MRI) and will have the opportunity to re-start ocrelizumab treatment after birth and breastfeeding are over. The total duration of treatment period will be 192 weeks from the date of first dose of ocrelizumab, irrespective of how long the treatment was interrupted due to pregnancy.

Patients who plan to become pregnant during the study will be withheld from ocrelizumab treatment and will follow the recommendations for contraception period after the last infusion with ocrelizumab for at least 6 months or longer in accordance with locally applicable ocrelizumab package leaflet. Upon discontinuation of study treatment, these patients will enter the safety follow-up period but will not restart the study treatment.

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 *adverse event reporting* period *(defined in Section 5.3.1)*, 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 with a Pregnancy Outcome and Infant Health Information on First Year of life questionnaire provided by the Sponsor.

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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 48 weeks after the last dose of study drug*)*, if the event is believed to be related to prior *exposure to* study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Ocrelizumab IB

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.

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this open label, single arm study will be descriptive and primarily based on descriptive statistical methods. Unless otherwise specified, statistical tests will be exploratory in nature. Corresponding 95% CIs will be presented as appropriate. No correction for multiple testing will be applied.

Full details of all statistical aspects and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database and may include further exploratory analyses not explicitly described in this section, as well as analyses of data from the study phase beyond the main 192-week study period, e.g., safety follow-up information.

Analysis populations

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

ITT Population

All enrolled patients who received any dose of ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason will still be included in the ITT population.

PP Population

The PP population will include all ITT patients without protocol deviations deemed to affect the assessment of effectiveness. The list of criteria leading to exclusion from the PP population will be finalized prior to database closure and documented in the SAP.

Safety Population

The safety population will include all enrolled patients who received any dose or part of a dose of ocrelizumab.

6.1 DETERMINATION OF SAMPLE SIZE

The main study is a single-arm effectiveness and safety study. There is no formal statistical hypothesis and all analyses will be descriptive. The results for the key endpoints will be presented in a descriptive analysis including the corresponding 95% the confidence intervals.

Sample size considerations for the main study are based on pooled data from two ocrelizumab phase III trials in RRMS (OPERA I and II). Based on extrapolations from these studies, we can conservatively expect 15% of patients (or less) to have a CDP event and approximately the same number of patients to be prematurely withdrawn and censored before week 192.

In this case, for 1,100 patients, the precision (half-width of the 95% confidence interval) of the estimated CDP rate by study end is expected to be approximately 1.8%, i.e., the 95% confidence interval of (13.2%, 16.8%).

In OPERA the EDSS improvement at 2 years had a standard deviation of 0.74, based on 240 patients from the ocrelizumab group, who were previously treatment-naïve with disease duration ≤3 years and EDSS ≤3.5. The standard deviation was rather stable over time and is assumed to remain stable after four years of treatment. A sample size of 1,100 patients is expected to provide a precision for the estimate of the EDSS change from baseline of about 0.037, assuming a standard deviation of 0.75. Assuming no EDSS change from baseline, the 95% confidence interval is expected to be (-0.074, 0.074).

The main study was initially planned to enroll at least 600 patients. Approximately 550 additional patients were to be enrolled in the shorter infusion sub-study. They would also be enrolled in the main study (see Appendix 10 for more details). Therefore, the main study would enroll a total of at least 1,100 patients. A total of 1,225 patients (678 in the main study and 547 in the shorter infusion substudy) were enrolled in the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, screening failures, ocrelizumab administration, and discontinuations from the study will be summarized using descriptive statistics (frequency tables for categorical endpoints and mean, median, range, standard, deviation [SD] and 25^{th}-75^{th} quartiles for the continuous endpoints). Patient disposition and the incidence of treatment discontinuation for different reasons will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics (age, gender, and self-reported race), medical history and neurological examination will be summarized. The following will also be summarized: MS disease history (duration since first MS symptoms, duration of MS since diagnosis, relapses in the past year), baseline measures of MRI, EDSS and other important variables.

6.4 EFFECTIVENESS ANALYSES

6.4.1 Effectiveness Endpoints

Effectiveness of ocrelizumab will be evaluated by means of a set of endpoints addressing different facets of MS. There is no primary endpoint defined in the main study. These effectiveness endpoints include time to onset of confirmed CDP sustained for at least 24 and 48 weeks, change from baseline in EDSS score over time, relapse rates, MRI-based measures of disease activity and progression or degeneration, measures of cognition and PROs.

For a full list of effectiveness endpoints refer to Section 2

After the Week 192 visit of the last enrolled patient, approximately *24 weeks and* 48 weeks may be needed to allow the confirmation of the last event of the *24-week and* 48 week-CDP (CDP/CDI confirmation visit). The main study analysis will be performed after the last CDP and CDI confirmation visit. *With respect to CDP confirmation visits, only EDSS data at all the visits occurring in the treatment period of the study and LTE study (for patients who roll over to study MN39158) will be used. Appropriate statistical methods to account for missing confirmation visits will be defined in the SAP.*

The evaluation of the clinical effectiveness of ocrelizumab will be based upon the events and assessments in-between baseline and week 192.

For patients who do not have an event by week 192, the time-to-event endpoints will be censored at the time of last visit in the study. A descriptive analysis based on the Kaplan-Meier method will be performed for the time to CDP and other time-to-event endpoints, such as the time to first relapse or the time to first event of disease activity. Cox proportional hazards regression will be used to identify predictors for CDP and other time-to-event endpoints. Variables to be included in the regression model will be region, gender, baseline EDSS, and some other variables, as appropriate. Further details will be specified in the SAP.

The change from baseline in EDSS, as well as other continuous variables, will be primarily analyzed using descriptive statistics, the mean, corresponding 95% CI, standard deviation and other statistics will be presented. Furthermore, the change of EDSS from baseline to each visit will be analyzed by linear mixed models for repeated measures (MMRM) adjusting for covariates such as the respective baseline score, geographical region, and baseline EDSS.

MRI activity will be evaluated from week 8 (baseline for MRI-based endpoints) to week 192.

For binary endpoints, e.g., NEP, NEDA and NEPAD, the proportion of patients meeting the endpoint at Week 96, 144 and 192 will be calculated and the corresponding two-sided Clopper-Pearson 95% CI will be presented. Logistic regression models will be used to identify prognostic factors.

The annualized relapse rates will be analyzed using a Poisson regression model, adjusting for region and baseline EDSS. The total number of T1 Gd-enhanced lesions will be calculated as the sum of the individual number of T1 Gd-enhanced lesions at Weeks 24, 48, 96, 144 and 192. A Poisson model will be used to estimate the rate of lesion occurrence. A quasi Poisson or negative binomial regression may be applied as a sensitivity analysis.

An analysis of individual components of the composite endpoint will also be performed.

6.4.2 Exploratory Endpoints

The exploratory effectiveness objective for the main study is to further assess the effectiveness of ocrelizumab 600 mg IV given every 24 weeks by monitoring endpoints as listed in Section 2.

The exploratory endpoints will be summarized descriptively and using methods similar to those used for the other effectiveness endpoints. Full details of the derivations and analyses of exploratory endpoints will be provided in the SAP.

6.5 SAFETY ANALYSES

6.5.1 Safety Outcome Measures

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

6.5.2 Safety Analyses

The safety analysis will be performed on Safety population. Safety will be assessed through summaries of adverse events (including rates/incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities.

All adverse events occurring on or after treatment on Day 1will be summarized by mapped term, appropriate thesaurus level and toxicity grade, and tabulated by body system and Preferred Term for individual adverse events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from the study due to an adverse event, first adverse event leading to infusion adjustment, and time to first selected treatment-

related adverse event will be summarized. In addition, all serious adverse events and deaths will be listed.

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

Ocrelizumab exposure will be summarized, including duration and dosage.

Concomitant medications recorded during the study will be summarized by frequency tables.

6.6 OTHER ANALYSIS

Other information, including, but not limited to, ADA, JCV, and biomarker endpoints will be analyzed. *Exploratory immunology analyses of SARS-CoV-2 antibody titers and SARS-CoV-2 T cell responses will be analyzed* as appropriate and details will be specified in a separate Biomarker Analysis Plan.

6.7 SUBGROUP ANALYSIS

Some effectiveness analyses may be undertaken in specific patient subgroups, for example, female patients interrupting treatment due to pregnancy. Details of these subgroup analyses will be presented in the SAP.

6.8 HANDLING OF MISSING DATA

Patients not completing the study for reasons different from lack of effectiveness or death will be defined as not reaching the NEDA endpoint (“NEDA=no”). The same rule will be used for NEP and NEPAD. More details about the missing data handling will be specified in statistical analysis plan.

6.9 INTERIM ANALYSIS

No formal effectiveness interim analyses are planned. Exploratory analyses of selected endpoints (including CDP and safety analysis) will be performed during the course of the study, for example, after all patients have completed the first 48 weeks of the treatment phase and the necessary data are available. In addition, an interim analysis will be performed after completion of the core part of the shorter infusion substudy (see Appendix 10).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. Central imaging review 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 at the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the PRO questionnaires as well as the BICAMS scoring data received from the central reader will be entered into the EDC system by site staff.

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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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 (US) or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) *to communicate information that might affect a patient's willingness to continue* in the study, the patients or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor *has* implement*ed* a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identif*ied* potential risks associated with critical trial processes and data and implement*ed* plans for evaluating and controlling these risks. Risk evaluation and control include*d* the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits *are* provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Roche, and will be managed by Roche and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

*For the shorter infusion substudy, a*n Independent Data Monitoring Committee (iDMC) will be employed to monitor the incidence of IRR and perform additional unblinded safety analyses during the study as described in the iDMC charter.

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

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

9.6 DISSEMINATION 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. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 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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APPENDICES

APPENDIX 1
Schedule of Assessments: Screening through the End of Treatment Period

Visit	Screening	Treatment Period [a]											Early study treatment discontinuation evaluation	*Safety* Follow-Up 48 weeks after *the last infusion* [b] Refer to Appendix 2
	1	2 (Baseline)	3	4	5	6	7	8	9	10	11	12		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)	120 (±14 days)	144 (±14 days)	168 (±14 days)	192 (±14 days)		
Informed consent [c]	X													
Medical history and demographic data [d]	X													
Review inclusion & exclusion criteria	X	X												
Physical examination [e]	X	X	X		X	X	X	X	X	X	X	X	X	
Height and weight	X													
Vital signs [f]	X	X	X		X	X	X	X	X	X	X	X	X	
PROs		X			X	X		X		X		X	X	
Brain MRI [g]	X			X	X	X		X		X		X	X	
Laboratory assessments														

Visit	Screening	Treatment Period											Early study treatment discontinuation evaluation	*Safety* Follow-Up 48 weeks after *the last infusion* [b] Refer to Appendix 2
	1	2 (Baseline)	3	4	5	6	7	8	9	10	11	12		
Week	**–4 to –1 weeks**	**1**	**2 (±2 days)**	**8 (±3 days)**	**24 (±14 days)**	**48 (±14 days)**	**72 (±14 days)**	**96 (±14 days)**	**120 (±14 days)**	**144 (±14 days)**	**168 (±14 days)**	**192 (±14 days)**		
Hematology, chemistry, urinalysis [h]	X	X	X		X	X	X	X	X	X	X	X	X	
Pregnancy test [i]	X	X	X		X	X	X	X	X	X	X	X		
Hepatitis screening [j]	X													
Hepatitis B virus DNA test [j]	X													
Lymphocytes subtypes sample [k]		X	X		X	X	X	X	X	X	X	X	X	
Serum for NfL [l]		X				X		X		X		X	X	
Optional blood for DNA (RBR) [m]		X												
ADA [n]		X			X	X	X	X					X	
Ocrelizumab concentration [n]		X			X	X	X	X					X	
Optional whole blood & serum samples for SARS-CoV-2 vaccine immunological assessments [o]	*Please see Figure 3 for details.*													
EDSS score [p]	X	X			X	X	X	X	X	X	X	X	X	

Visit	Screening	Treatment Period											Early study treatment discontinuation evaluation	*Safety* Follow-Up 48 weeks after *the last infusion* [b] Refer to Appendix 2
	1	2 (Baseline)	3	4	5	6	7	8	9	10	11	12		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)	120 (±14 days)	144 (±14 days)	168 (±14 days)	192 (±14 days)		
MSFC		X			X	X	X	X	X	X	X	X	X	
Neurological examination [q]	X	X	X		X	X	X	X	X	X	X	X	X	
BICAMS assessment		X				X		X		X		X		
Recording of potential relapses		X	X		X	X	X	X	X	X	X	X	X	
Adverse event assessment [r]		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant treatment review		X	X		X	X	X	X	X	X	X	X		
Methylprednisolone and antihistaminic drug premedication [s]		X	X		X	X	X	X	X	X	X			
Ocrelizumab administration [t]		X	X		X	X	X	X	X	X	X			
Telephone contact every 8 weeks [u]													(X)	

ADA = Anti-drug antibodies; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BICAMS= Brief International Cognitive Assessment for Multiple Sclerosis; *CDI = Confirmed disability improvement; CDP = Confirmed disability progression; DMT = disease modifying treatment;* eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; ICF = Informed consent form; IRR = Infusion-related reaction; IV = intravenous; LTE = Long-term extension; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; NfL = neurofilament light chain; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; RBC = red blood cell; RBR = Research Biosample Repository; *SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SoA = schedule of assessments;* WBC = white blood cell.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The study visits during the treatment period may be spread over more than one day to complete all the assessments before study drug administration.

[b] *Patients who discontinue treatment early for any reason and patients who complete the 192-week Treatment Period and do not continue in a separate LTE study will be followed up for 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for MS, they will be discontinued from the study.* Patients who discontinue study treatment and switch to commercially marketed ocrelizumab, either after completion of the 192 weeks Treatment Period or after early discontinuation of the 192 weeks Treatment Period, will not enter the safety Follow-up Period.

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

[d] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 6 weeks prior to the screening visit. Demographic data will include age, sex, self-reported race/ethnicity, and educational level.

[e] A complete physical examination should be performed at the screening and baseline visits and at all dosing visits during treatment. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF.

[f] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent). In addition, vital signs should be obtained prior to the ocrelizumab infusion, then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. Vital signs will be reported in the eCRF only in case of an IRR. Record abnormalities observed before enrolment on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] The MRI scans should be obtained within 14 days prior to next ocrelizumab infusion and should be reviewed by local/treating investigator for safety reasons before dosing with ocrelizumab. The MRI should be approved by the Medical Image Analysis Centre for efficacy evaluation before dosing with ocrelizumab.

[h] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, creatinine, total bilirubin, random glucose, potassium and sodium. Urine dipstick will be done at site locally.

[i] Serum b-hCG must be performed at screening in women of childbearing potential. Subsequently, urine β-hCG (sensitivity $\geq$ 25 mIU/mL) must be collected. On infusion visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of childbearing potential. If positive, ocrelizumab should be withheld. The FSH test is only applicable to confirm postmenopausal status in female patients.

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

[k] Lymphocytes subtypes samples should be collected prior to ocrelizumab infusion to screen for CD19+, T-cell counts (CD4+, CD8+), and other cell subsets at the local laboratory.

[l] Serum sample to include but not be limited to measurement of NfL, will be collected prior to the IV methylprednisolone infusion *(if obtained on the days of ocrelizumab infusion)* at baseline and repeated every 48 weeks *according to SoA,* and will be analyzed at central laboratory.

[m] Optional whole blood sample for RBR DNA is only collected from patients who sign the separate consent for storage and research use of their samples (RBR ICF). If the sample is not collected at baseline, the sample can be collected at any visit.

[n] Serum samples are collected prior to the methylprednisolone infusion for 2 years of treatment for each patient. **Following 2 years, samples should only be collected in any event of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction as close as possible to the event and then at 4- and 16-weeks post-dose.**

[o] *Whole blood and serum samples collected on the day of the infusion must be collected prior to the IV methylprednisolone administered as premedication. Samples will be collected up to 18 months following the last dose of vaccine.*

[p] Patients must have an EDSS score of 0.0 to 3.5 points, inclusive at screening to be eligible. *After the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24-week and 48-week CDP (CDP/CDI confirmation visit). For those patients presenting with an EDSS change at the end of the treatment period and who roll over to the LTE study (Study MN39158), the 24-week and 48-week CDP confirmation visits will occur during the LTE study (Study MN39158). For patients who discontinue the study (e.g., move onto commercial ocrelizumab, or start treatment with another DMT), the EDSS CDP confirmatory assessments will not be performed.*

[q] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. Investigators will also screen patients for signs and symptoms of PML by evaluating 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). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study.

[r] Adverse events will be reported throughout the study and until 48 weeks after the last dose of ocrelizumab as provided during the study period. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Sections 5.3.1 and 5.6). At the end of treatment evaluation, reasons for study discontinuation will be captured via telephone call unless a site visit is requested by the investigator.

[s] All patients must receive prophylactic treatment with 100 mg methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes and not less than 25 minutes prior to each ocrelizumab infusion and an antihistamine, via oral, intramuscular or IV route to be completed approximately 30-60 minutes and not less than 25 minutes prior to before each infusion of ocrelizumab (the antihistamine should be the first premedication to be administered). The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

[t] Ocrelizumab will be administered as two 300-mg IV infusions in 250 mL 0.9% sodium chloride each on Days 1 and 15 and one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks ±14 days) for a maximum of 168 weeks. It is anticipated that the patient will need to stay at the hospital or clinic for the infusion visits. Patients will be allowed to switch from the conventional ocrelizumab infusion (~3.5 hours) to the shorter ocrelizumab infusion (~2.0 hours) at any visit after the Week 24 visit, based on the schedules of infusion as per the protocol, after providing written informed consent and in agreement with their treating physician, provided they have not experienced any previous serious IRRs with ocrelizumab treatment. While on the shorter infusion, the patients can switch back to the conventional infusion, in agreement with their treating physician. If patients develop a serious IRR while on the shorter infusion, they will be switched to the conventional infusion and should not be restarted on the shorter infusion at any following infusion visit.

[u] A structured telephone interview will be conducted by site personnel every 8 weeks (± 3 days), starting after the site visit at 8 weeks to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections. No telephone contact is needed in weeks where patient is performing on-site visits (week 24, 48, 72, 96, etc.).

Note: *All l*ab samples can be taken up to 2 weeks prior to the scheduled study visit. Local laboratory results for hematology, biochemistry and CD4 should be available prior to dosing as they are re-treatment criteria. Local laboratory results for CD8 and CD19 may be available later, as they do not need to be verified prior to re-treatment. Samples for NfL, ADA, and ocrelizumab concentration are collected and sent to the central laboratory for analysis.

APPENDIX 2
Safety Follow-up Schedule of Assessments

Patients who discontinue treatment early for any reason and patients who complete the the 192 weeks Treatment Period and do not continue in a separate long-term extension (LTE) study will be followed up for 48 weeks after the last infusion of the study drug. When patients begin an alternative treatment for multiple sclerosis (MS), they will be discontinued from the study.
Patients who discontinue study treatment and switch to commercially marketed ocrelizumab, either after completion of the 192 weeks Treatment Period or after early discontinuation of the 192 weeks Treatment Period, will not enter the safety Follow-up Period.

	***Safety* Follow Up**		
	Patients who complete the Treatment Period	***Patients who discontinue treatment early***	
Assessment	*Week 48 after the last infusion of study drug* (±14 days)	*Week 24 after the last infusion of study drug* (±14 days)	*Week 48 after the last infusion of study drug (±14 days)*
Routine safety laboratory tests [a]	X	X	*X*
Lymphocytes subtypes [b]	X	X	*X*
Vital signs	X	X	*X*
EDSS score [c]	X	*X*	*X*
Potential relapses recorded	X	X	*X*
Adverse events [d]	X	X	*X*
Concomitant medication	X	X	*X*

CDI = Confirmed disability improvement; CDP = Confirmed disability progression; EDSS = Expanded Disability Status Scale; MS = Multiple sclerosis

[a] Routine safety lab: hematology, chemistry and urinalysis.

[b] Lymphocytes subtypes samples for CD19+, T-cell counts (CD4+, CD8+), and other cell subsets.

[c] *After the end of treatment period visit of the last enrolled patient, approximately 24 weeks and 48 weeks may be needed to allow the confirmation of the last event of the 24-week and 48-week CDP (CDP/CDI confirmation visit).*

[d] Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. Unrelated SAEs must be collected and reported during the study through the end of the Safety Follow-Up Period, which is 48 weeks after the last infusion. Non-serious adverse events have to be reported until the end of Safety Follow-up Period *(see Sections 5.3.1 and 5.6).*

APPENDIX 3
Expanded Disability Status Scale (EDSS)

EDSS steps	
0	*Normal neurological exam (all FS grade 0)*
1.0	*No disability, minimal signs in one FS (one FS grade 1)*
1.5	*No disability, minimal signs in more than one FS (more than one FS grade 1)*
2.0	*Minimal disability in one FS (one FS grade 2, others 0 or 1)*
2.5	*Minimal disability in two FS (two FS grade 2, others 0 or 1)*
3.0	*Fully ambulatory but with moderate disability in one FS (one FS grade 3, others 0 or 1)* ***OR*** *Fully ambulatory but with mild disability in three or four FS (three / four FS grade 2, others 0 or 1)*
3.5	*Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1;* ***OR*** *Fully ambulatory with two FS grade 3 (others 0 or 1);* ***OR*** *Fully ambulatory with five FS grade 2 (others 0 or 1)*
4.0	***Fully ambulatory for ≥500 meters without aid or rest****; up and about some 12 hours a day characterised by relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps*
4.5	***Ambulatory for 300 - 500 meters without aid or rest****; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps*
5.0	***Ambulatory for 200 - 300 meters without aid or rest*** *(usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)*
5.5	***Ambulatory for 100 - 200 meters without aid or rest***
6.0	***Ambulatory for at least 100 meters with intermittent or constant unilateral assistance*** *(cane or crutch) with or without rest* ***OR*** *Ambulatory < 100 meters without help or assistance* ***OR*** *Ambulatory ≥ 50 meters with unilateral assistance* ***OR*** *Ambulatory ≥ 120 meters with bilateral assistance*
6.5	***Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches)*** *without rest* ***OR*** *Ambulatory for < 50 meters with unilateral assistance (cane or crutch)* ***OR*** *Ambulatory 5 to 120 meters with constant bilateral assistance (canes or crutches)*
7.0	***Unable to walk 5 meters even with aid, essentially restricted to wheelchair****; wheels self and transfers alone; up and about in wheelchair some 12 hours a day*
7.5	***Unable to take more than a few steps; restricted to wheelchair****; may need some help in transferring and in wheeling self*
8.0	***Essentially restricted to bed or chair or perambulated in wheelchair****, but out of bed most of day; retains many self-care functions; generally has effective use of arms*
8.5	***Essentially restricted to bed much of the day****; has some effective use of arm(s); retains some self-care functions*
9.0	*Helpless bed patient; can communicate and eat*
9.5	*Totally helpless bed patient; unable to communicate effectively or eat/swallow*
10	*Death due to MS*

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

Functional System Scores

1. Visual FSS

0	*normal*
1	*disc pallor and / or small scotoma and / or visual acuity (corrected) of worse eye less than 20 / 20 (1.0) but better than 20 / 30 (0.67)*
2	*worse eye with maximal visual acuity (corrected) of 20 / 30 to 20 / 59 (0.67 – 0.34)*
3	*worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20 / 60 to 20 / 99 (0.33 – 0.21)*
4	*worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20 / 100 to 20 / 200 (0.2 – 0.1); grade 3 plus maximal acuity of better eye of 20 / 60 (0.33) or less*
5	*worse eye with maximal visual acuity (corrected) less than 20 / 200 (0.1); grade 4 plus maximal acuity of better eye of 20 / 60 (0.33) or less*
6	*grade 5 plus maximal visual acuity of better eye of 20 / 60 (0.33) or less*

2. Brainstem FSS

0	*normal*
1	*signs only*
2	*moderate nystagmus and / or moderate EOM impairment and / or other mild disability*
3	*severe nystagmus and / or marked EOM impairment and / or moderate disability of other cranial nerves*
4	*marked dysarthria and / or other marked disability*
5	*inability to swallow or speak*

3. Pyramidal FSS

0	*normal*
1	*abnormal signs without disability*
2	***minimal disability**: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups*
3	***mild to moderate paraparesis or hemiparesis**: BMRC grade 4 in >two muscle groups; and/or **BMRC grade 3 in one or two muscle groups** (movements against gravity are possible); and/or **Severe monoparesis**: BMRC grade 2 or less in one muscle group*
4	***marked paraparesis or hemiparesis:** usually BMRC grade 2 in two limbs and/or **monoplegia:** BMRC grade 0 or 1 in one limb; and/or **moderate tetraparesis:** BMRC grade 3 in ≥ three limbs*
5	***paraplegia**: BMRC grade 0 or 1 in all muscle groups of the lower limbs; and/or **marked tetraparesis:** BMRC grade 2 or less in ≥ three limbs; and/or **hemiplegia***
6	***tetraplegia**: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs*

4. Cerebellar FSS

0	*normal*
1	*abnormal signs without disability*
2	*mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible*
3	*moderate limb ataxia and/or moderate or severe gait/truncal ataxia*
4	*severe gait/truncal ataxia and severe ataxia in three or four limbs*
5	*unable to perform coordinated movements due to ataxia*
X	*pyramidal weakness (BMRC grade ≤3) or sensory deficits interfere with cerebellar testing*

5. Sensory FSS

0	*normal*
1	*mild vibration or figure-writing or temperature decrease only in 1 or 2 limbs*
2	*mild decrease in touch / pain / position sense or moderate decrease in vibration in 1 or 2 limbs and/or mild vibration or figure-writing or temperature decrease alone in more than 2 limbs*
3	*moderate decrease in touch / pain / position sense or marked reduction in vibration in 1 or 2 limbs and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in > 2 limbs*
4	*marked decrease in touch or pain in 1 or 2 limbs and/or moderate decrease in touch or pain and/or marked reduction of proprioception > 2 limbs*
5	*loss (essentially) of sensation in one or two limbs and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head*
6	*sensation essentially lost below the head*

6. Bowel/Bladder FSS

0	*normal*
1	*mild urinary hesitancy, urgency **and/or** constipation*
2	*moderate urinary hesitancy/retention **and/or** moderate urinary urgency/incontinence **and/or** moderate bowel dysfunction*
3	*frequent urinary incontinence or intermittent self-catheterisation; needs enema or manual measures to evacuate bowels*
4	*in need of almost constant catheterization*
5	*loss of bladder or bowel function; external or indwelling catheter*
6	*loss of bowel and bladder function*

7. Cerebral FSS

0	*normal*
1	*signs only in decrease in mentation; mild fatigue*
2	*mild decrease in mentation; moderate or severe fatigue*
3	*moderate decrease in mentation*
4	*marked decrease in mentation*
6	*dementia*

8. Ambulation score

0	*unrestricted*
1	*Fully ambulatory ≥ 500 meters without help or assistance but not unrestricted (pyramidal or cerebellar FS ≥ 2)*
2	*Ambulatory ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0, defined by FSS)*
3	*Ambulatory ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)*
4	*Ambulatory ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)*
5	*Ambulatory < 100 meters without help or assistance (EDSS 6.0)*
6	*Ambulatory ≥ 50 meters with unilateral assistance (EDSS 6.0)*
7	*Ambulatory ≥ 120 meters with bilateral assistance (EDSS 6.0)*
8	*Ambulatory < 50 meters with unilateral assistance (EDSS 6.5)*
9	*Ambulatory ≥ 5 meters, but < 120 meters with bilateral assistance, (EDSS 6.5)*
10	*Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)*
11	*Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)*
12	*essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)*

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

APPENDIX 4
Telephone Interviews

The purpose of this interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms). Telephone interviews should be performed by study personnel every 8 weeks between clinic visits (see also Section 4.5.11)

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 related to multiple sclerosis (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 an infection?		
3. Since your last visit or telephone interview, have you had any other new or worsening medical problems or conditions (including pregnancy)?		
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 Treating Investigator and review
patient's answers. The Investigator can determine if an unscheduled visit is required.

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

_____
__
_____
__
_____
__

NAME: _____ Date: _____
Name of person completing the telephone interview

APPENDIX 4
Telephone Interviews (cont.)

Below is a sample list of medications that can weaken the immune system. This list
does not include all drugs that can suppress the immune system.
The patient should not take or have taken any of the here below mentioned therapies

Approved MS Therapies:

Glatiramer acetate (Copaxone®)
Interferon ß-1a (Rebif®, AVONEX®)
Interferon ß-1b (Betaseron®)
Mitoxantrone (Novantrone®)
Natalizumab (Tysabri®)
Fingolimod (Gilenya®) – if relevant
Daclizumab (Zinbryta®)
Alemtuzumab (Lemtrada®)

Immunosuppressants/Antineoplastics:

Azathioprine (Imuran®, Azasan®)
Cladribine (Leustatin®)
Cyclophosphamide (Cytoxan®, Neosar®)
Cyclosporine (Sandimmune®, Neoral®)
Fludarabine phosphate (Fludara®)
Leflunomide (Arava®)
Mercaptopurine (Purinethol®)
Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
Mycophenolate mofetil (CellCept®)
Pemetrexed (Alimta®)

Additional Immunomodulators and Immunosuppressants:

Other interferons (Actimmune®, Infergen®, Intron® A,
Pegasys®, PEG-Intron®, Rebetron®, Roferon®-A)
Adalimumab (Humira®)
Alefacept (Amevive®)
Alemtuzumab (Campath®)
Anakinra (Kineret®)
Daclizumab (Zenapax®)
Etanercept (Enbrel®)
Infliximab (Remicade®)
Intravenous immunoglobulin (IVIG)
Ofatumumab (Arzerra®)
Rituximab (Rituxan/MabThera®)
Trastuzumab (Herceptin®)

APPENDIX 5
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action steps if progressive multifocal leukoencephalopathy (PML) is suspected:

- If the clinical presentation is suggestive of PML, further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 1), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of John Cunningham virus (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.

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

MRI Assessment

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

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

CSF Assessment

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

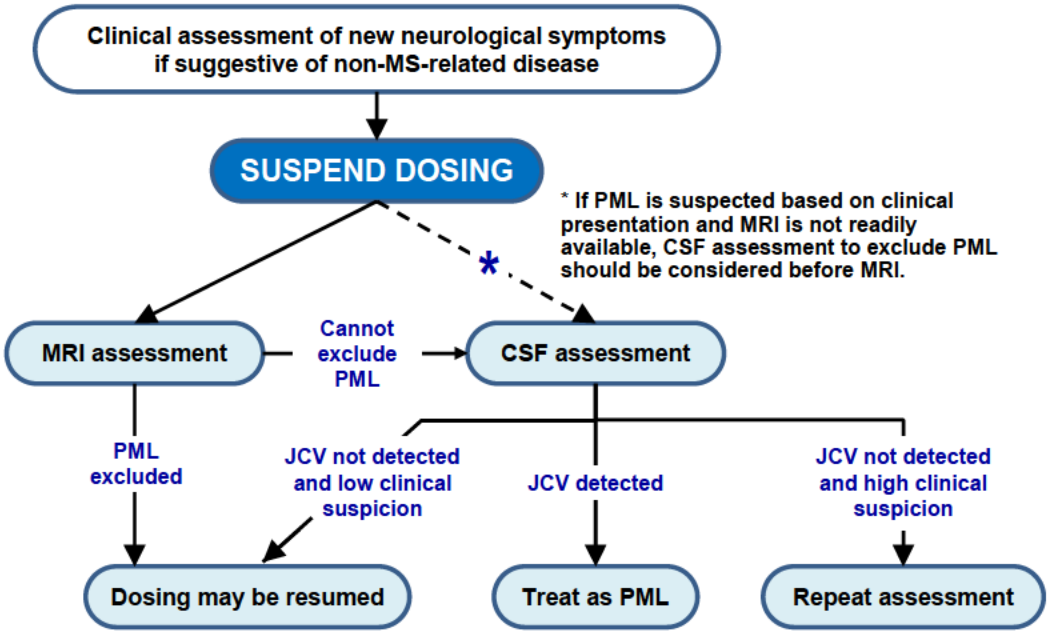
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.

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

APPENDIX 5
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Figure 1 Diagnostic Algorithm for PML

Suggested Diagnostic Algorithm



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

Table 1 Clinical Sings and Symptoms Typical of MS and PML*

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

* Adapted from Kappos L et al. 2007

APPENDIX 5
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy (cont.)

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal 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
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

Adapted from Yousry TA et al. 2006

APPENDIX 6
Patient Reported Outcomes

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2)

UK original of MSIS-29 v2

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past two weeks, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving about indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Heavy arms and/or legs?	1	2	3	4
9. Tremor of your arms or legs?	1	2	3	4
10. Spasms in your limbs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2) continued

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the toilet urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short-tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2)

UK original of MSIS-29 v2

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past two weeks, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving about indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Heavy arms and/or legs?	1	2	3	4
9. Tremor of your arms or legs?	1	2	3	4
10. Spasms in your limbs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2) continued

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the toilet urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short-tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis V2.0 (WPAI:MS)

The following questions ask about the effect of your multiple sclerosis on your ability to work and perform normal daily activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, tick "NO" and skip to question 6.

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your multiple sclerosis? Include hours you missed on sick days, times you went in late, left early, etc., because of your multiple sclerosis. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS (If "0", skip to question 6)

5. During the past seven days, how much did your multiple sclerosis affect your productivity <u>while you were working</u>?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If multiple sclerosis affected your work only a little, choose a low number. Choose a high number if multiple sclerosis affected your work a great deal.

Consider only how much multiple sclerosis affected productivity <u>while you were working</u>.

Multiple sclerosis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your multiple sclerosis affect your ability to perform your normal daily activities, other than work at a job?

   By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If multiple sclerosis affected your activities only a little, choose a low number. Choose a high number if multiple sclerosis affected your activities a great deal.

Consider only how much multiple sclerosis affected your ability to do your normal daily activities, other than work at a job.

Multiple sclerosis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65.

SYMPTOM SCREEN

Please circle **one number that best describes how MS has affected each function.** For example, if it takes you longer to type or text, you might rate your hand function as 'mildly limited' (circle '2'), but if you gave up typing completely, you might rate your hand function as 'very limited' (circle '4').

	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5- very severe limitation/ I'm unable to do many daily activities	6 – total limitation/ I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Achiness, tenderness	0	1	2	3	4	5	6
Sensory symptoms Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress; panic attacks	0	1	2	3	4	5	6

APPENDIX 7
Pregnancy Outcome and Infant Health Information on First Year of Life

Pregnancy Outcome and Infant Health Information on First Year of Life

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

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

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

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

Table 2: Information on birth

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

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
Growth alteration *- Yes ☐* *- No ☐*	*☐ Small for gestational age (SGA)* *☐ Low birth weight* *☐ Short birth length*	*If Growth alteration present::* *Specify weight:_____:* *Specify length:_____*	*Contributing factors:*
Congenital anomalies *- Yes ☐* *- No ☐*	*☐ Major structural malformation* *A defect that has either cosmetic or functional significance to the child*	*Specify: _____* _____ _____	*Contributing factors:* _____ _____
	☐ Minor structural malformation *A defect that occurs infrequently but has neither cosmetic nor functional*	*Specify: _____* _____	*Contributing factors:* _____

	significance to the child	_____	_____
	☐ *Deformation* *A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)*	*Specify:* _____ _____ _____	*Contributing factors:* _____ _____
	☐ *Disruption* *A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)*	*Specify:* _____ _____ _____	*Contributing factors:* _____ _____
Functional deficit (except for infections, which should be described in separate table below) *- Yes* ☐ *- No* ☐	☐ *Functional deficit*	*Specify:* _____ _____ _____	*Contributing factors:* _____ _____

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

Table 4: Status of infant

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

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ *Yes*
☐ *No*
☐ *Unknown*

If available, please provide CD19 count (B cell values) at birth (regardless of infection)?

☐ *normal*
☐ *abnormal*
☐ *unknown*

If abnormal, specify test result: _____
If abnormal, date of test: _____

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.
If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.
If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on infection in neonate at birth

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

Neutrophil count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Lymphocyte count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Other, specify:	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____

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

Maternal risk factors for neonatal infection	***Date of diagnosis***	***If diagnosed, was pregnant mother treated with anti-infective prior to delivery?***	
☐ *Maternal intrapartum colonisation or infection with group B streptococcus (GBS)* ☐ *Maternal listeriosis* ☐ *Premature rupture of membranes (PROM)* ☐ *Meconium in amniotic fluid (meconium-stained liquid)* ☐ *Active genital herpes infection* ☐ *CMV* ☐ *HPV (papilloma virus)* ☐ *Other, specify*	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____	
Relevant laboratory test results in pregnant mother:			
CD19 count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
IgG levels	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
White blood cell count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____

Neutrophil count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Lymphocyte count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Other, specify: *(e.g. any specific antibodies and their titers)*	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____

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

☐ *Yes*

☐ *No*

☐ *Unknown*

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

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

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

CD19 count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
IgG levels	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
White blood cell count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Neutrophil count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Lymphocyte count	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____
Other, specify:	☐ *normal* ☐ *abnormal* ☐ *unknown*	*If abnormal, specify test result:* _____	*If abnormal, date of test:* _____

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

Vaccinations administered at birth and during first year of age	***Date administered***	***Infant's age on day of vaccination***	***Comments (abnormal outcome, reason for postponing vaccination, etc)***
☐ *Hepatitis B*			
☐ *Rotavirus*			
☐ *Diphtheria, tetanus, and pertussis*			
☐ *Haemophilus influenzae type b*			
☐ *Pneumococcal*			

☐ *Poliovirus* ☐ *Attenuated oral Polio vaccine* ☐ *Inactivated Polio vaccine*			
☐ *Meningococcal group B bacteria*			
☐ *Tuberculosis (Bacille Calmette Guérin, BCG) bacteria*			
☐ *Other vaccination, specify:* _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

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

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

Please enter text in the free text box below:

APPENDIX 8
T and B Cells Impact Substudy Protocol

T AND B CELLS IMPACT SUBSTUDY PROTOCOL

TITLE:	**A SUBSTUDY TO EVALUATE THE INDIRECT IMPACT OF OCRELIZUMAB ON THE T AND B CELL IMMUNE SYSTEM IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS** ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	MA30143 T and B cells Impact Substudy for France
VERSION NUMBER:	*6*.0 (for France)
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

T and B Cells Impact Substudy PROTOCOL ACCEPTANCE FORM

TITLE:	**A SUBSTUDY TO EVALUATE THE INDIRECT IMPACT OF OCRELIZUMAB ON THE T AND B CELL IMMUNE SYSTEM IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS** ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
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IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature | Date

Co-Investigator's Name (print)

Co-Investigator's Signature | Date

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

T AND B CELLS IMPACT SUBSTUDY PROTOCOL SYNOPSIS

TITLE:	**A SUBSTUDY TO EVALUATE THE INDIRECT IMPACT OF OCRELIZUMAB ON THE T AND B CELL IMMUNE SYSTEM IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS** ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	MA30143 T and B cells Impact Substudy for France
VERSION NUMBER:	*6*.0 (for France)
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
PHASE:	IIIb
INDICATION:	Relapsing-Remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

B cell depletion by ocrelizumab has recently demonstrated efficacy in the treatment of RMS and PPMS. The aim of this substudy is to decipher the impact of B cell depletion by ocrelizumab on T cells and B cells subsets and functions before and after treatment with ocrelizumab. This substudy will obtain blood from patients enrolled in the main study MA30143 to assess:

T cell subsets, functionalities such as cytokine production and migration capacities but also repertoire and transcriptome, and B cells subsets, functionalities such as cytokine production, differentiation capacities as well as B cell repertoire and genes expression before and after treatment with ocrelizumab. Moreover, biomarkers related to efficacy outcomes in this study population might emerge from this substudy.

Objectives	Corresponding endpoints
First objective:	
Part 1: **To evaluate the indirect impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients**	The following analyses will be performed at baseline, 24 weeks, 48 weeks and at the end of the study at 192 weeks or earlier in case of withdrawal from the study. These analyses will also be performed in case of extra visit due to relapse if applicable. • Analysis of general immune cells frequencies in blood including B cells, T cells, dendritic cells, monocytes and NK cells subsets. Markers will include, but are not limited to CD4, CD8, CD19, CD11c, CD56, CD14, and CD16. • Analysis of CD4+ and CD8+ T cells subset frequencies including naïve, central memory, effector memory or TEMRA subsets at baseline, 24, 48 and 192 weeks of ocrelizumab treatment. • Analysis of CD4+ and CD8+ T cells phenotype including regulatory and effector (Tc1, Tc17, Th1, Th17) subsets. Markers used include, but are not limited to CD3, CD4, CD8, CD161, CD45RC, CD127, IL18Ra, CXCR6, EOMES, PLZF1, perforin, GZB, CCR5, CCR6, CD25, CCR2, MCAM, DNAM, CD39, LFA1, PSGL1, VLA4, IFN-γ, IL-17, IL-22, Foxp3, Rorγt, or Tbet. • Analysis of T cells activation of sorted blood CD4+ and CD8+ T cells in vitro by measurement of cytokine production. Cytokines, including, but not limited to GM-CSF, IFN- γ, IL-17, IL-22, IL-13, will be assessed by flow cytometry stainings in CD4+ or CD8+ T cells after 5 days of total PBMCs (Peripheral Blood Mononuclear Cells) stimulation with anti-CD3 and anti-CD28. Quantitative measurements of a large panel of cytokines and chemokines in culture supernatant will be performed using luminex technology. • Analysis of transmigration capacities of CD4+ and CD8+ T cells across an experimental model of Blood-Brain-Barrier in resting or inflammatory conditions. • Analysis of T cell repertoire in sorted CD4+ and CD8+ T cells using high throughput sequencing (Illumina Miseq). This analysis will be performed on the first 20 patients' samples and will not be performed at 24 weeks. • Analysis of RNA sequencing in sorted CD4+ and CD8+ T cells using Illumina assays. This analysis will be performed on the first 20 patients samples and will not be performed at 24 weeks. Indirect impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients will be measured by change from baseline for each marker and for each time point.

Objectives	Corresponding endpoints
Part 2: **To decipher the indirect impact of ocrelizumab on B cell repopulation**	Two periods can be defined: - B cell depletion period on ocrelizumab - B cell repletion off ocrelizumab. During B cell depletion period (weeks 24, 48 and 192, or study withdrawal visit), analyses will be performed only in partially repleted patients (below the lower limit of normal) with sufficient amount of B cells applicable for each analysis as described below. During B cell repletion period off ocrelizumab, analyses will be performed in partially repleted patients with sufficient amount of B cells and in repleted patients i.e. in patients having peripheral B cell level at or above the lower limit of normal. These analyses will also be performed in case of extra visit due to relapse in patients with sufficient amount of B cells. • Analysis of the proportions of the different B cell subsets in peripheral blood. Different markers will be used to distinguish switched/unswitched memory, mature naïve, transitional B cells, plasmablasts and plasmocytes (CD19, CD20, CD27, IgD, CD38, CD24, CD138). Activated markers will also be determined (CD95, MHC-II, CD80, CD86). ➢ 1.10^4 B cells per sample would trigger this analysis. • Analysis of the different B cell subsets will also be realized after some short (48h) stimulation protocols. We will evaluate the frequencies of regulatory and effector B cells after stimulation using flow cytometry. Cytokines such as IL-10, GZM B, TGF b and IL-35 (for regulatory cells) but also TNFa, GM-CSF, LT and IL-6 (for effector B cells) will be measured. Quantitative measurements of a large panel of cytokines and chemokines in culture supernatant will be performed using luminex technology. ➢ This part will only be performed if there are enough B cells i.e. at least 5.10^5 to 1.10^6 per sample. • Analysis of the differentiation abilities of B cells using a differentiation protocol lasting 6 days, already published (Chesneau et al, 2015). ➢ This part will only be performed if there are enough B cells in the peripheral blood i.e. at least 3.10^6 per sample. • Analysis of B cell repertoire in sorted B cells by immunosequencing (Adaptive biotechnologies) to assess immune reconstitution to establish correlations with clinical outcome. ➢ 1.10^3 B cells per sample would trigger this analysis. • Analysis in reconstituted B cells of the expression of a panel of 96 genes (including surface markers, transcription factors, and cytokines) at the single cell level using parallel qPCR reactions (microfluidic technologies). ➢ 5.10^3 B per sample cells would trigger this analysis. Thresholds mentioned for B cells analysis may be adjusted according to investigators decision and sampling procedures. In any cases, all analyses will describe the initial cell frequencies in study samples. Indirect impact of ocrelizumab-dependent B cell depletion on B cell subsets and functions in naïve RRMS patients will be measured by change from baseline for each marker and for each time point.

Objectives	Corresponding endpoints
Second objective:	
To assess the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.	• Relationship between any B cells subset, $CD4^+$ or $CD8^+$ T cell subset or immunological marker at baseline, 24, 48, 192 weeks or earlier in case of withdrawal from the study of ocrelizumab treatment or during relapses and core study efficacy and safety objectives of MA30143 core study (endpoints). For instance, neurological markers that will be correlated with interesting immunological markers identified in the first part, will include, but will not be limited to: - Total number of T1 Gd-enhancing lesions as detected by brain MRI over time - Total number of new and/or enlarging T2 lesions as detected by brain MRI over time - Change in T1 volume over time - Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time - Time to first relapse - Change from baseline in EDSS score over the course of the study Relationship between any biomarkers with any other biomarker.

Study Design

Description of Study

This substudy is a longitudinal, multi-center, substudy of the Phase IIIb ocrelizumab trial MA30143.

This substudy will evaluate the indirect impact of ocrelizumab-dependent B cell depletion on T and B cell subsets and functions in naïve RRMS patients, during B cell depletion and during B cell repletion period off ocrelizumab.

This substudy will help to assess the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.

Patients who provide consent to participate in this substudy and fulfill eligibility criteria will provide additional blood samples at baseline, 24 weeks, 48 weeks, end of treatment period (192 weeks or earlier in case of study withdrawal), every 24 weeks *for 48 weeks* after last *infusion of* ocrelizumab and in case of unscheduled visit due to relapse, as indicated in the schedule of assessments.

Blood samples can be collected 2 weeks (± 4 days) prior to ocrelizumab infusion, in addition to laboratory samples required in the main study.

12 tubes of 8mL each will be drawn at each time points. Samples will be prepared and frozen at investigational centers and sent to Nantes CHU for in vitro analyses.

Number of Patients

The number of patients enrolled in this MA30143 substudy is ~ 50 patients. Patients enrolled in study MA30143 and recruited in specific centers in France will be offered to participate in this substudy.

Participating centers are restricted to French investigator centers with PBMC (peripheral blood mononuclear cell) technical and storage capacity.

The number of patients that will withdraw from the study is estimated to be 10 (20% withdrawal rate over 192 weeks). As a consequence, approximately 10 patients would enter the follow-up period for B cell repletion. Patients will provide blood samples every 24 weeks *for 48 weeks* after last ocrelizumab infusion.

Target Population

Inclusion Criteria

Patients must meet the following criteria to be eligible for substudy entry:

- Enrolled in the Phase IIIb study MA30143
- Signed Informed Consent Form for the MA30143-T and B cell Substudy France
- Able to comply with the substudy protocol, in the investigator's judgment.

Exclusion Criteria

There is no exclusion criteria beyond those listed in the main protocol of the MA30143 study.

End and length of the substudy

The end of the substudy is defined as the last patient visit. *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*

The maximum length of the study, from screening of the first patient to the end of the substudy, is expected to be approximately *316* weeks (6*.5* years). This includes an enrolment period of approximately 76 weeks.

Investigational Medicinal Products

No IMP is specifically distributed for this substudy. In core MA30143 protocol, the first dose of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg IV infusion in 500 mL 0.9% sodium chloride every subsequent doses (i.e., every 24 weeks ±14 days) for a maximum of 8 doses.

Statistical Methods

Due to the small sample size, the substudy data analysis will be descriptive only.

If relevant, calculated confidence intervals will be displayed with a 95% level.

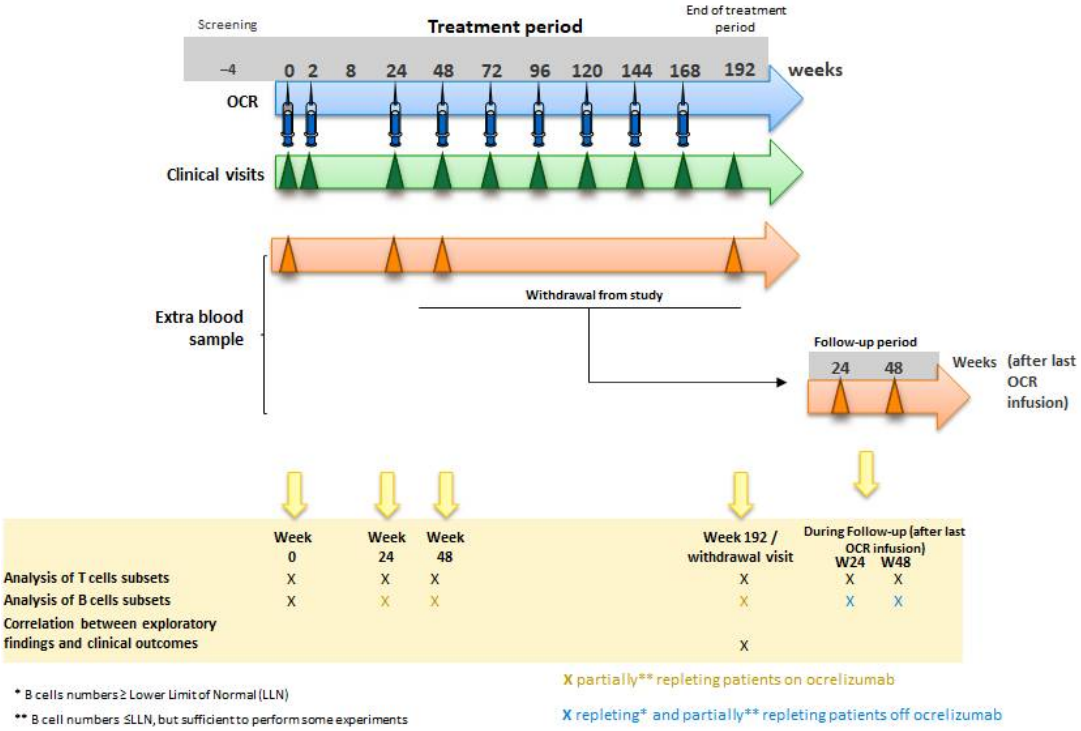
Indirect impact of ocrelizumab-dependent B cell depletion on T cell and B cell subsets and functions in naïve RRMS patients will be measured by the change from baseline for each marker and for each time point.

Relationship between biomarkers will be evaluated using correlation coefficient at each endpoint (linear and non-linear correlation will be searched).

Relationship between any B cells or T cell subsets (or any immunological marker at any time point) and core study efficacy and safety objectives will be performed using a regression model to evaluate biomarkers predictive factors of efficacy or safety objectives.

Full details of the derivations and analyses of exploratory endpoints will be detailed in the corresponding substudy Statistical Analysis Plan.

Substudy Design



Schedule of Assessments

Visit	Screening	Treatment Period					*Safety* Follow-up period	Unscheduled Visits	
	1	2 (Baseline)	5	6	12	Early study treatment discontinuation visit		relapse 1	relapse 2
Week	-4 to -1 wks	1	24 (±14 days)	48 (±14 days)	192 (±14 days)		Visits Every 24 weeks (+/- 14 days) (*for 48 weeks* after last dose)		
Substudy Inform Consent	X								
Blood Collection for Substudy		X	X	X	X	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARR	Annualized Relapse Rate
BRC	Biological Resource Center
CD	Cluster of Differentiation
CDP	Confirmed Disability Progression
CHU	Centre Hospitalier Universitaire (University Hospital)
CI	Confidence Interval
CNS	Central Nervous System
CPT	Cell Preparation Tube
CSF	Cerebro-Spinal Fluid
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
FC	Flow Cytometry
FSS	Functional Systems Score
HC	Healthy Control
HR	Hazard ratio
IB	Investigator's Brochure
Ig	Immunoglobulin
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NK	Natural Killer
OCBs	Oligoclonal Bands
OFSEP	French Observatory for Multiple Sclerosis
PBMCs	Peripheral Blood Mononuclear Cells
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SAP	Statistical Analysis Plan
SPMS	Secondary Progressive Multiple Sclerosis
TEMRA	$CD45RA^+$ effector memory T cells

T AND B CELLS IMPACT SUBSTUDY PROTOCOL

BACKGROUND

Background on Multiple Sclerosis and ocrelizumab

Multiple sclerosis (MS) is a chronic, demyelinating and degenerative disease of the central nervous system (CNS) whose epidemiology, subtypes and symptoms are described in the main protocol (MA30143).

Multiple Sclerosis is characterized by active demyelinating areas called lesions or plaques, CNS lesions in MS typically present immune cell infiltration and inflammation which are absent in normal brain tissue. Macrophages dominate the infiltrate, followed by CD8+ T cells, whereas lower numbers of CD4+ T cells, B cells and plasma cells can also be found. Resident cells also contribute to the disease pathophysiology and microglial cells and astrocytes are activated in the CNS (Dendrou, Fugger, and Friese 2015). Although the T cell composition of infiltrates does not differ as the disease develops, the relative proportion of B cells and plasma cells increases (Frischer et al. 2009).

Humoral immunity has been implicated in MS for decades, as evidenced by inclusion of Cerebrospinal Fluid (CSF) oligoclonal bands (OCBs) and increased Immunoglobulin G (IgG) index in diagnostic criteria for MS (Polman et al. 2011; Siden 1979).

Until very recently, the prevailing view of MS pathophysiology held that the CNS inflammation seen in MS is principally mediated by proinflammatory T cells.

However, rapidly expanding evidence suggests that B cells may contribute to MS pathogenesis much more fundamentally than was previously believed, potentially through either antibody dependent or independent mechanisms (Meinl, Krumbholz, and Hohlfeld 2006; Franciotta et al. 2008; McFarland 2008). B lymphocytes have been detected within MS lesions and in the CSF of patients with MS.

B cells are thought to play an important role in the pathogenesis of multiple sclerosis by:

- Presenting auto-antigens and co-stimulatory signals to activate T cells (Constant 1999; Crawford et al. 2006; Harp et al. 2010)
- Secreting pro-inflammatory cytokines at greater relative proportions than protective cytokines (Bar-Or et al. 2010; Barr et al. 2012; Duddy et al. 2007; Li, Rezk, Healy, et al. 2015; Li, Rezk, Miyazaki, et al. 2015)
- Producing auto-antibodies which may cause tissue damage and activate macrophages (Genain et al. 1999; Storch et al. 1998)
- Creating meningeal lymphoid follicle-like structures, linked to microglia activation, local inflammation and neuronal loss in the nearby cortex (Magliozzi et al. 2010; Serafini et al. 2004)

As a consequence, B cell targeting represents an interesting therapeutic approach in MS.

Ocrelizumab is a recombinant human monoclonal antibody that selectively targets and eliminates CD20+ B cells. In two phase III clinical trials in RMS, ocrelizumab has demonstrated superior efficacy over subcutaneous IFNβ-1a. Please refer to main protocol and Investigator Brochure for information regarding efficacy and safety of ocrelizumab in RMS patients.

Rationale for the substudy

Recent clinical trials in MS have shown the high efficacy of anti-CD20 mAbs in relapsing-remitting MS patients on inflammatory parameters. The efficacy of the treatment is seen as soon as 12 weeks after treatment onset (Hauser et al. 2008) and does not modify the presence of oligoclonal bands in the CSF (Cross et al. 2006), indicating that the efficacy is not due to a direct effect on antibody production. B cells account for less than 5% of immune infiltrate in the CSF (Cepok et al. 2005) and are found in MS patient's lesions in lower numbers than T cells (10 times lower) or macrophages/microglial cells (Frischer et al. 2009). Therefore, it is hypothesized that the effect of anti-CD20 may be linked to antibody-independent effects of B cells via cytokine secretion by B cells or antigen presentation to T cells possibly in periphery.

It has been demonstrated that B cell depletion by anti-CD20 mAb influence T cells. For example, it has been shown that the use of anti-CD20 mAb modifies the amount of T cells in the CSF of patients (Cross et al. 2006; Piccio et al. 2010) and hypothetically in MS lesions. This hypothesis is supported by the reduction of T cell infiltration in the Experimental Autoimmune Encephalomyelitis (EAE) rat model of MS when the animals are treated with anti-CD20 mAb (Anthony et al. 2014). However, if B cell depletion by ocrelizumab does not seem to influence T cells numbers it is hypothesized that ocrelizumab-induced B cell depletion might exert its beneficial effect in MS by influencing T cells subsets, phenotype and/or functions. It is not known whether the indirect T cell effect of ocrelizumab could be more pronounced on CD4 or CD8 T cells and in which subtypes of these T cells. It is also unknown whether ocrelizumab-induced B cell depletion modifies T cell repertoire or transcriptome, and impacts their functional ability to secrete specific cytokines (IL17, IFNg) or to migrate through the blood brain barrier.

T cells subsets ($CD4^+$ and $CD8^+$ T cells) are thought to play a central role in MS immunopathophysiology. $CD4^+$ T cells, and in particular Th1 and Th17 inflammatory subsets have been well studied in EAE mouse models (Fletcher et al. 2010) and both Th1 and Th17 cells are able to transfer EAE in mice although pathologies induced differ in terms of histopathological features and immune profile, suggesting complementary roles (Kroenke et al. 2008). Th1 and Th17 cells role in human pathology has been similarly suggested (Fletcher et al. 2010). For instance, IL-17 producing cells (including Th17 cells, but also glial cells and $CD8^+$ T cells) were identified in active rather than inactive areas of MS lesions (Tzartos et al. 2008) and increased Th17 cells in blood of MS patients are associated with disease activity (Durelli et al. 2009). Moreover, $IFN\gamma^+$ IL-17^+ double positive T cells are enriched in MS brain tissue, suggesting a pathogenic role for those cells (Kebir et al. 2009). On the contrary, many studies have suggested that Tregs immunosuppressive functions are impaired in MS patients (Fletcher et al. 2010; Dendrou, Fugger, and Friese 2015).

$CD8^+$ T cells seem to be particularly implicated in the disease process (Friese and Fugger 2009; Goverman 2009). They appear to be more numerous in MS patients brain lesions than other T cell subtypes and $CD8^+$ T cell infiltrates within CNS lesions were frequently oligoclonally expanded, (Babbe et al. 2000; Junker et al. 2007; Montes et al. 2009; Skulina et al. 2004). Interestingly, the same clones were found in different lesion sites and even in the normal appearing white matter (Junker et al. 2007; Montes et al. 2009; Salou, Garcia, et al. 2015; Salou, Nicol, et al. 2015),

suggesting that few antigens may drive T cell response in the central nervous system (CNS). Looking at blood and CSF in MS patients, peripheral T cell repertoire was regularly skewed as compared to healthy controls (HC) repertoire (Gestri et al. 2001; Laplaud et al. 2004; Matsumoto et al. 2003; Muraro et al. 2002). Altogether, these arguments suggest a direct involvement of $CD8^+$ T cells in the pathophysiological process of the disease. However, the precise role of these cells, i.e. the reasons for their entry into the CNS, and their antigen specificity remains to be determined.

B cells are quickly depleted after anti-CD20 therapies (within 14 days after ocrelizumab treatment, see IB). Studies using Rituximab have shown that repleting B cells after the end of treatment exhibit a naïve phenotype ($CD27^-$ B cells) (Duddy et al. 2007; Palanichamy et al. 2014) and are less inflammatory than before depletion. For instance, after reconstitution, B cells secrete less inflammatory cytokines such as IL-6 or GM-CSF and more anti-inflammatory cytokines (IL-10) after in vitro stimulation than before depletion by rituximab (Barr et al. 2012; Duddy et al. 2007; Li, Rezk, Miyazaki, et al. 2015).

Therefore, the purpose of this substudy is to analyze B and T cells subsets during and after ocrelizumab-induced B cell depletion in order to better understand ocrelizumab mechanism of action.

Benefits / risk assessment

The results of this substudy are expected to help to better understand the mechanism of action of ocrelizumab in naïve RRMS patients. The substudy will particularly analyze the direct effects of ocrelizumab on B cells subsets and functions before and after repletion and its indirect effects on CD4+ and CD8+ T cells subsets and functions.

This substudy does not induce any major additional risk to the main study as it does not add any visit or procedure to the main study. Extra blood samples will be collected in addition to the blood laboratory samples planned in the main study.

Objectives and Endpoints

The objectives of this substudy are to evaluate the impact of ocrelizumab-dependent B cell depletion on T and B cell subsets and functions in naïve RRMS patients, during B cell depletion and repletion.

This substudy will help to assess the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.

T and B cells will be analyzed both before, during (on partially repleted patients for B cell analysis) and after (on partially repleted and repleted patients for B cell analysis) treatment with ocrelizumab. Specific objectives and corresponding endpoints for the substudy are outlined below.

Objectives	Corresponding endpoints
First objective:	
Part 1: **To evaluate the indirect impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients**	The following analyses will be performed at baseline, 24 weeks, 48 weeks and at the end of the study at 192 weeks or earlier in case of withdrawal from the study. These analyses will also be performed in case of extra visit due to relapse if applicable. • Analysis of general immune cells frequencies in blood including B cells, T cells, dendritic cells, monocytes and NK cells subsets. Markers will include, but are not limited to CD4, CD8, CD19, CD11c, CD56, CD14, and CD16. • Analysis of $CD4^+$ and $CD8^+$ T cells subset frequencies including naïve, central memory, effector memory or TEMRA subsets. • Analysis of $CD4^+$ and $CD8^+$ T cells phenotype including regulatory and effector (Tc1, Tc17, Th1, Th17) subsets. Markers used include, but are not limited to CD3, CD4, CD8, CD161, CD45RC, CD127, IL18Ra, CXCR6, EOMES, PLZF1, perforin, GZB, CCR5, CCR6, CD25, CCR2, MCAM, DNAM, CD39, LFA1, PSGL1, VLA4, IFN-γ, IL-17, IL-22, Foxp3, Rorγt, or Tbet. • Analysis of T cells activation of sorted blood $CD4^+$ and $CD8^+$ T cells in vitro by measuring cytokine production. Cytokines, including, but not limited to GM-CSF, IFN- γ, IL-17, IL-22, IL-13, will be assessed by flow cytometry stainings in $CD4^+$ or $CD8^+$ T cells after 5 days of total PBMCs (Peripheral Blood Mononuclear Cells) stimulation with anti-CD3 and anti-CD28. Quantitative measurements of a large panel of cytokines and chemokines in culture supernatant will be performed using luminex technology. Cytokines and chemokines analyzed will include GM-CSF, IL-1β, IL-5, IL-4, IL-2, TNF-α, IL-6, RANTES, MIG, VEGF, HGF, EGF, IL-8, IL-17, MIP-1α, IL-10, G-CSF, MCP-1, IL-7, IL-15, IFN-α, IL-2R, IP-10, MIP-1β, Eotaxin, IL-1RA, IL-12 (p40/p70) IL-13, FGF-Basic, IFN-γ. • Analysis of transmigration capacities of $CD4^+$ and $CD8^+$ T cells across an experimental model of Blood-Brain-Barrier in resting or inflammatory conditions. • Analysis of T cell repertoire in sorted $CD4^+$ and $CD8^+$ T cells using high throughput sequencing (Illumina Miseq). This analysis will be performed on the first 20 patients' samples and will not be performed at 24 weeks. • Analysis of RNA sequencing in sorted $CD4^+$ and $CD8^+$ T cells using Illumina assays. This analysis will be performed on the first 20 patients' samples and will not be performed at 24 weeks. Indirect impact of ocrelizumab-dependent B cell depletion on T cell subsets and functions in naïve RRMS patients will be measured by change from baseline for each marker and for each time point.

Part 2: **To decipher the indirect impact of ocrelizumab on B cell repopulation**	Two periods can be defined: - B cell depletion period on ocrelizumab - B cell repletion off ocrelizumab. During B cell depletion period (weeks 24, 48 and 192, or study withdrawal visit), analyses will be performed only in partially repleted patients with sufficient amount of B cells applicable for each analysis as described below. During B cell repletion period off ocrelizumab, analyses will be performed in partially repleted patients with sufficient amount of B cells and in repleted patients i.e. in patients having peripheral B cell level at or above the lower limit of normal. These analyses will also be performed in case of extra visit due to relapse in patients with sufficient amount of B cells. • Analysis of the proportions of the different B cell subsets in peripheral blood. Different markers will be used to distinguish switched/unswitched memory, mature naïve, transitional B cells, plasmablasts and plasmocytes (CD19, CD20, CD27, IgD, CD38, CD24, CD138). Activated markers will also be determined (CD95, MHC-II, CD80, CD86). ➢ 1.10^4 B cells per sample would trigger this analysis. • Analysis of the different B cell subsets will also be realized after some short (48h) stimulation protocols. We will evaluate the frequencies of regulatory and effector B cells after stimulation using flow cytometry. Cytokines such as IL-10, GZM B, TGF b and IL-35 (for regulatory cells) but also TNFa, GM-CSF, LT and IL-6 (for effector B cells) will be measured. Quantitative measurements of a large panel of cytokines and chemokines in culture supernatant will be performed using luminex technology. ➢ This part will only be performed if there is enough B cells i.e. at least 5.10^5 to 1.10^6 per sample. • Analysis of the differentiation abilities of B cells using a differentiation protocol lasting 6 days, already published (Chesneau et al, 2015). ➢ This part will only be performed if there is enough B cells in the peripheral blood i.e. at least 3.10^6 per sample. • Analysis of B cell repertoire in sorted B cells by immunosequencing (Adaptive biotechnologies) to assess immune reconstitution to establish correlations with clinical outcome. ➢ 1.10^3 B cells per sample would trigger this analysis. • Analysis in reconstituted B cells of the expression of a panel of 96 genes (including surface markers, transcription factors, and cytokines) at the single cell level using parallel qPCR reactions (microfluidic technologies). ➢ 5.10^3 B per sample cells would trigger this analysis. Thresholds mentioned for B cells analysis may be adjusted according to investigators decision and sampling procedures. In any cases, all analyses will describe the initial cell frequencies in study samples. Indirect impact of ocrelizumab-dependent B cell depletion on B cell subsets and functions in naïve RRMS patients will be measured by change from baseline for each marker and for each time point.

Objectives	Corresponding endpoints
Second objective:	
To assess the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.	• Relationship between any B cells subset, $CD4^+$ or $CD8^+$ T cell subset or immunological marker at baseline, 24, 48, 192 weeks or earlier in case of withdrawal from the study of ocrelizumab treatment or during relapses and core study efficacy and safety objectives of MA30143 core study (endpoints). For instance, neurological markers that will be correlated with interesting immunological markers identified in the first part, will include, but will not be limited to: - Total number of T1 Gd-enhancing lesions as detected by brain MRI over time - Total number of new and/or enlarging T2 lesions as detected by brain MRI over time - Change in T1 volume over time - Change in brain volume (including white and grey matter fractions) as detected by brain MRI over time - Time to first relapse - Change from baseline in EDSS score over the course of the study • Relationship between any biomarkers with any other biomarker.

STUDY DESIGN

Description of the substudy

This substudy is a longitudinal, multi-center, substudy of the Phase IIIb ocrelizumab trial MA30143.

This substudy will evaluate the indirect impact of ocrelizumab-dependent B cell depletion on T and B cell subsets and functions in naïve RRMS patients, during B cell depletion and during B cell repletion period off ocrelizumab. This substudy will help to assess the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.

Patients who provide consent to participate in this substudy and fulfill eligibility criteria will provide additional 12x8 mL blood samples at baseline, 24 weeks, 48 weeks, end of treatment period (192 weeks or earlier in case of study withdrawal), and every 24 weeks *for 48 weeks* after last ocrelizumab infusion and in case of unscheduled visit due to relapse, as indicated in the schedule of assessments.

Blood samples can be collected 2 weeks (± 4 days) prior ocrelizumab infusion, in addition to laboratory samples required in the main study.

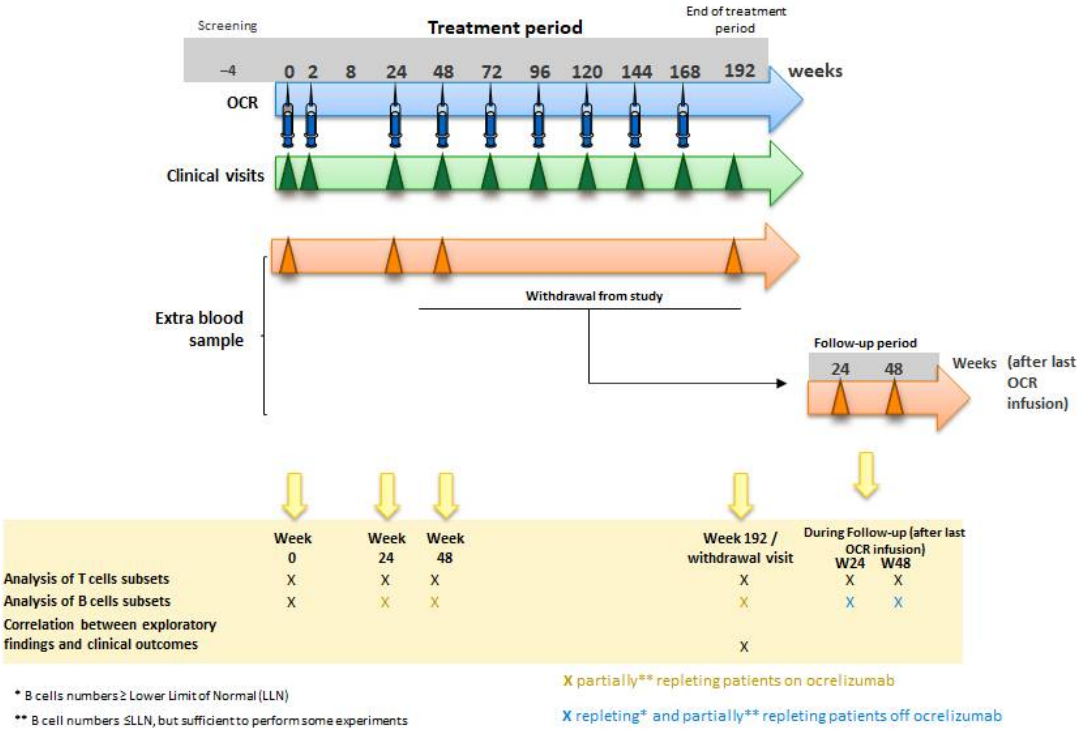
About 50 patients from specific centers in France enrolled in MA30143 study will be offered to participate in this substudy.

The number of patients that will withdraw from the study is estimated to be 10 (20% withdrawal rate over 192 weeks). As a consequence, approximatively 10 patients would enter the follow-up period for B cell repletion. Patients will provide blood samples every 24 weeks *for 48 weeks* after *the* last ocrelizumab infusion.

Overview of study design

Figure 1 presents an overview of the substudy procedures. A schedule of assessments is provided in Appendix 1.

Figure 1 Overview of Study design



Procedure in case of visit for relapse

In case of unscheduled visit due to a core protocol defined relapse between the weeks 24 and 192 of the study, additional blood sample will be collected (12 x 8mL). This additional blood collection will not occur more than two times for a patient. Extra blood samples will not be collected in case of relapse within the first 24 weeks or during the follow-up.

End and length of substudy

The end of the substudy is defined as the last patient visit *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*

The maximum length of the study, from first patient screening to the end of the substudy, is expected to be approximatively *316* weeks (6.*5* years). This includes an enrolment period of approximately 76 weeks.

Centers

The substudy will take place in France, in centers associated with an investigator centers with PBMC technical and storage capacity which can prepare samples for storage, using a similar standardized protocol in all the centers (see Appendix 2). Frozen samples will be shipped to the CHU of Nantes where they will be analyzed.

MATERIALS AND METHODS

Patients

Patients with early stage RRMS who fulfill eligibility criteria for the Phase IIIb study (MA30143) and the eligibility criteria outlined in the following inclusion and exclusion sections of this substudy can be enrolled into the substudy. Approximately 50 patients are planned to be enrolled in the substudy.

Inclusion Criteria

Patients must meet the following criteria to be eligible for substudy entry:

- Enrolled in the Phase IIIb study MA30143
- Signed Informed Consent Form for the MA30143-T and B cell Substudy
- Able to comply with the substudy protocol, in the investigator's judgment.

Exclusion Criteria

There is no exclusion criteria beyond those listed in the main protocol of the MA30143 study.

Substudy assessments

Procedure for enrolment of eligible patients

All patients eligible for the main study are also eligible to enter in the substudy, if desired.

Patients must sign and date the most current Institutional Review Board/Institutional Ethics Committee's (IRB/IEC) approved written informed consent form for the main study in which they are participating (MA30143) and a separate informed consent form for the substudy before any substudy-specific assessments or procedures are performed.

Sample Collection and visits assessments

Visits for this substudy will occur at the same time as visits for the main study (see Appendix 1).

Patients who have enrolled in the main study and enrolled in this optional research substudy will have additional substudy blood specimens collected at each time point as outlined in the schedule of assessments (Appendix 1).

Twelve samples of 8 mL of whole blood (96 mL) will be collected in CPT tubes. Samples will be processed and frozen in the investigator centers with PBMC technical and storage capacity and stored before shipment to the CHU of Nantes where experiments will be performed.

Each center is responsible for collection, preparation, freezing, storage and shipment of samples to Nantes CHU every 6 months.

Leftovers of processed specimens, which will consist of frozen cells, will be retained for a maximum of 5 years after the end of the trial (for confirmation of results). CHU of Nantes will destroy those samples once the study report of the substudy has been finalized.

Patient, Study and site discontinuation

Patient discontinuation

Patients have the right to voluntarily withdraw from the substudy at any time for any reason.

Patient's withdrawal from the substudy does not constitute a withdrawal from the main trial. Patients withdrawal from main study and/or substudy does not, by itself constitute withdrawal of specimens already collected for the substudy. Consent for further research to be performed on collected specimens as part of the substudy may be withdrawn at any time and collected samples destroyed, by contacting the sponsor, which will ask the CHU of Nantes to destroy the samples.

No replacement for patients who withdraw from the substudy is planned.

Study and Site Discontinuation

The Sponsor has the right to terminate the main study or to close a site at any time. Reasons for termination are listed in the main study protocol (MA30143). The Sponsor will notify the investigators if the Sponsor decides to discontinue the study. Consequently, the substudy could be stopped.

The Sponsor has also the right to terminate this substudy at any time.

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

ASSESSMENT OF SAFETY

Safety assessment

Adverse events related to the substudy procedure will be collected throughout the substudy according the same procedure of the main study protocol, as outlined in the main study protocol (MA30193).

Blood draw may have procedural adverse events such as minor discomfort, lightheadedness, or bruising at the draw site. If any AE occurs in regards to the procedure for this substudy sample, it should be reported according to the main study protocol instructions in Sections 5.3 and 5.4.

Safety instructions and guidance

Safety measures regarding the study medication are not part of this substudy, and are detailed in the main protocol (MA30143).

Reporting of Adverse Events

If an adverse event specifically related to the substudy procedure occurs, it will be recorded in the e-CRF and documented in the study report.

Reporting of Serious Adverse Events

Refer to Section 5.4.2 of main protocol.

Emergency Medical Contacts

Refer to Section 5.4.1 of main protocol.

STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Due to the small sample size, the substudy data analysis will be descriptive only.

The number of patients expected to participate in this optional substudy is ~ 50.

Estimation for a proportion of 50%, with a study size of 50, the precision of the estimation is 13.9%.

If relevant, calculated confidence intervals will be displayed with a 95% level.

All variables will be summarized in statistical tables including the following descriptive statistics:

- The quantitative variables will be described using the number of non-missing values, the number of missing values, the mean, the standard deviation, the median, the first and the third quartiles, the minimum and the maximum.
- The qualitative variables will be described using the number of non-missing values, the number of missing values, the frequency and the percentage per modality.

Full details of the derivations and analyses of exploratory endpoints will be detailed in the corresponding substudy Statistical Analysis Plan (SAP). The SAP will be written by the Sponsor in accordance with the investigator coordinator of this substudy.

These data are intended to be hypothesis-generating, and are not expected to achieve statistical significance. Data generated as part of this substudy will be described in a separate clinical study report.

Evaluation of the impact of ocrelizumab-dependent B cell depletion on T and B cell subsets and functions in naïve RRMS patients, during B cell depletion and during B cell repletion period off ocrelizumab at the end of the treatment will be measured by the change from baseline for each marker and for each time point.

Assessment of the potential relationship between immunological biomarkers levels and clinical and/or subclinical change assessed by neurological markers will be measured using:

- Correlations between immunological markers and clinical outcome tested using linear and non-linear correlation coefficient.
- Relationship between any B cell subset, $CD4^+$ or $CD8^+$ T cell subsets (or any immunological marker at any time point) and core study efficacy objectives performed using a regression model to evaluate biomarkers predictive factors of efficacy or safety objectives.

Any additional exploratory analysis might be conducted and will be discussed with the investigator coordinator of this substudy before being described in the SAP

DATA COLLECTION AND MANAGEMENT

Data collection and management

The overall procedures for quality assurance of clinical study data are described in the Sponsor's (or designee's) Standard Operational Procedures.

A contract research organization (CRO) will be responsible for data management of this substudy, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs (e.g. informed consent, withdrawal of consent, sample collection dates). Investigators will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the site, which the site will resolve electronically in the EDC system.

The sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Sponsor's standard procedures will be used to handle and process the electronic transfer of these data (including the non eCRF data). The clean database will be transferred to the Sponsor for analysis of the correlations with the clinical or subclinical efficacy and safety profile of the patients included in the substudy.

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

Substudy data will be recorded via the instrument used for data acquisition (flow cytometer, luminex technology, sequencing etc.) and for most experiments will be processed by CHU of Nantes to generate key data. These non eCRF data will be handled using the Sponsors standard procedures to handle and process these data.

Source data documentation

The Investigators shall supply the Sponsor on request with any required background data from the substudy documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

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.

Retention of records

Records and documents pertaining to the conduct of this substudy, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal

Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

ETHICAL CONSIDERATIONS

Compliance with Laws and Regulations

This study will be conducted in full conformance with the International Conference on Harmonization (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

Informed Consent

All patients must sign the informed consent form for the main study (MA30193) prior to screening. Additionally, all patients enrolled in this substudy must sign a separate informed consent form for collection of sample(s) prior to any substudy specific assessments.

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Caregiver Assent 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 investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with substudy procedures. 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 informed consent form will be required to document a patient's agreement to participate in substudy procedures.

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.

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.

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 Sponsor 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 sponsor 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. Sponsor is also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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.

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 or the patient's legally authorized representative, unless permitted or required by law.

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

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

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

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).

STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

Study Documentation and record keeping

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.

Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data. 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.

Administrative Structure

This trial will be sponsored by Roche, and will be managed by Roche and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

Publication of Data and Protection of Trade Secrets

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

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this substudy 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 results. If interim analysis of core study is done, correlation with substudy in a separate statistical report might be envisioned. 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.

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).

Appendices to Appendix 8

Appendix 1: Schedule of assessments

Visit	Screening	Treatment Period					*Safety* Follow-up period	Unscheduled Visits	
	1	2 (Baseline)	5	6	12	Early study treatment discontinuation visit		relapse 1	relapse 2
Week	-4 to -1 weeks	1	24 (±14 days)	48 (±14 days)	192 (±14 days)		Visits Every 24 weeks (+/- 14 days) (*for 48 weeks* after last dose)		
Substudy Inform Consent	X								
Blood Collection for Substudy		X	X	X	X	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)

Appendix 2: guidance for treatment of CPT tubes in OFSEP CRB
to be followed by investigator centers with PBMC technical and storage capacity

e) TRAITEMENT DES TUBES CPT (ANNEXE 5)

TUBES DE PRELEVEMENTS	MANIPULATION
 **Figure 9 : tubes CPT citrate sodium**	• Si possible, centrifuger **à 20°C** pendant **20 min** à **1800 g** sans frein dans les **2 h** après le prélèvement, après avoir remis le sang en suspension • Enlever délicatement 2 mL de plasma. • Remettre en suspension et conserver verticalement si besoin à température ambiante • Pooler le reste (l'anneau) contenant les **PBMC** dans un tube conique stérile en polypropylène de **50 mL** • Ajuster le volume à **45 mL** avec du **PBS 1X sans Mg^{++} ni Ca^{++}** (1^{er} lavage) • Centrifuger à **20°C** pendant 10 min à **330 g avec** frein • Eliminer le surnageant et ajuster le volume à **1 mL** avec du **MILIEU A** = suspension cellulaire • *Prélever* **20 µL** *pour effectuer la numération/viabilité à partir de la suspension cellulaire* • Rajouter **9 mL** de **PBS 1X sans Mg^{++} ni Ca^{++}** à la suspension cellulaire ($2^{ème}$ lavage) • Centrifuger à **20°C** pendant **10 min** à **330 g** avec frein • Eliminer le surnageant et ajuster le volume avec du **MILIEU A** pour avoir une concentration de **20 millions de cellules par mL** • Rajouter doucement le même volume de **MILIEU B** pour avoir une concentration de **10 millions de cellules par mL, dans la glace** • Réaliser **stérilement les échantillons** en fonction de la **numération** :

Numération = 40.10^6 cellules	4 échantillons de $10x10^6$cellules/mL
Numération = 35.10^6 cellules	3 échantillons de $10x10^6$cellules/mL+ 1 échantillon $5x10^6$cellules/mL
Numération < 30.10^6 cellules	2 échantillons de $10x10^6$cellules/mL + 1 échantillon supplémentaire
S'il reste moins de $3x10^6$ cellules, le rajouter au dernier échantillon	

• Congeler **IMMEDIATEMENT** dans une boîte à congélation progressive à **-80°C, isopropanol ou polystyrène (DMSO toxique pour les cellules à température ambiante)**
• Congeler les **échantillons** à **-196°C** dans l'azote liquide ou gazeux après **12 h minimum** à **-80°C**

Délai maximum de congélation 24 h. 72 h maximum à -80°C avant le transfert dans l'azote.

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APPENDIX 9
Immune Substudy Protocol

IMMUNE SUBSTUDY PROTOCOL

TITLE:	**A SUBSTUDY TO RESEARCH IMMUNOLOGICAL PARAMETERS AND SIGNATURES ASSOCIATED WITH OCRELIZUMAB TREATMENT IN EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS** ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	MA30143 Immune Substudy
VERSION NUMBER:	*6*.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. HOFFMANN-LA ROCHE LTD Grenzacherstrasse 124, 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp below

IMMUNE SUBSTUDY PROTOCOL ACCEPTANCE FORM

TITLE:	**A SUBSTUDY TO RESEARCH IMMUNOLOGICAL PARAMETERS AND SIGNATURES ASSOCIATED WITH OCRELIZUMAB TREATMENT IN EARLY STAGE RELAPSING-REMITTING MULTIPLE SCLEROSIS** ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	MA30143 Immune Substudy
VERSION NUMBER:	*6*.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature | Date

Co-Investigator's Name (print)

Co-Investigator's Signature | Date

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

IMMUNE SUBSTUDY PROTOCOL SYNOPSIS

TITLE:	A SUBSTUDY TO RESEARCH IMMUNOLOGICAL PARAMETERS AND SIGNATURES ASSOCIATED WITH OCRELIZUMAB TREATMENT IN EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS ASSOCIATED WITH MA30143 CORE STUDY: AN OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	MA30143 Immune Substudy
VERSION NUMBER:	*6*.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
PHASE:	IIIb
INDICATION:	Relapsing-Remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objective	To explore immunological changes associated with ocrelizumab treatment in a treatment naïve, early stage MS population. This substudy will help to assess the potential relationship between immunological biomarker levels and clinical and/or subclinical changes assessed by neurological markers in naïve RRMS patients treated with ocrelizumab.
Study design	This study is designed as a substudy to the MA30143 prospective, multicenter, open-label and single-arm effectiveness and safety study on ocrelizumab in patients with early stage RRMS. Patients giving their consent to participate in this substudy will be asked to provide 6 x 9 mL EDTA blood and 1 x 9 mL serum samples (total blood volume of 63 mL) at baseline, *week 24, week 48, week 96, week 192/or early treatment discontinuation visit* and at *48 weeks* after *the last infusion of ocrelizumab* Additional samples (6 x *9* mL EDTA blood and 1 x *9* mL serum samples [total blood volume of *63* mL]) will be collected, wherever possible, in cases of relapse, de novo vaccination or severe infection. Blood and serum samples will be collected, processed and stored at indicated time points aligning with the MA30143 study. Clinical and radiological parameters will be derived from the MA30143 trial and correlated with the immunological parameters measured in the substudy.

Study duration	**Length of Substudy** The total length of the substudy is aligned with the main study. Total length of the parent study, from screening of the first patient to the end of the study, is expected to be approximately *356* weeks (~7 years). This includes an enrolment period of 116 weeks. **End of Substudy** The substudy end is defined as the last patient last visit *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*
Study population	**Inclusion Criteria** Patients must meet the inclusion criteria stated in the MA30143 parent study protocol. In addition, following criteria have to be met for substudy entry: • Signed informed consent form for the substudy • Able to comply with the substudy protocol, in the investigator's judgment **Exclusion Criteria** There are no exclusion criteria beyond those listed in the parent MA30143 study protocol. **Number of Patients** This substudy will enroll approximately 80 patients.
Sites	Approximately 40 sites in Germany and other selected countries will be participating in this substudy.
Study Endpoints	**Basic Analysis (all evaluable Patients):** Frequencies of circulating immune cell subsets (B cells, T cells, NK cells, antigen presenting cells), measured relative to baseline (pre-infusion) at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab.* **Extended Analysis (first 30 enrolled Patients): Phenotypic and functional characterization** B cell and T cell expression of activation and lineage markers. Expression of phenotypic and activation markers on innate immune cells. T cell cytokine production. B and T cell proliferation, cytokine production and genetic immune receptor diversity. **Exploratory Associations:** Associations of immunological parameters with clinical, MRI, and safety parameters. For a comprehensive overview of assessed parameters see Tables 1, 2 and 3 in Section 2.

Statistical Methods

Each lymphocyte subset parameter will be summarized using descriptive statistics for patients at each scheduled time as well as change from baseline. Such summaries may include further summaries by patient subgroups. For each lymphocyte subset parameter, the change in lymphocyte subset parameter value for ocrelizumab treated relapsing-remitting multiple sclerosis (RRMS) patients after *week 24, week 48, week 96, week 192* from baseline will be analyzed using a linear mixed model. Confidence intervals will be interpreted in an exploratory manner.

Determination of Sample Size

No formal sample size determination was performed. The proposed numbers of patients are considered appropriate for this exploratory study and is consistent with other similarly conducted studies in the field (TERY-DYNAMIC Study Clinical trials.gov NCT01863888, Neurology April 5, 2016 vol. 86 no. 16 Suppl- P5.282)

Interim Analyses

Exploratory analyses of selected endpoints will be performed during the course of the study.

IMMUNE SUBSTUDY PROTOCOL

1 RATIONALE AND BENEFIT-RISK ASSESSMENT

1.1 RATIONALE

It is widely accepted that the clinical course of MS consists of two major phases; an early, focal inflammatory phase and a later, progressive phase characterized by neurodegeneration and CNS confined disseminated inflammation [1-5] Current DMTs work effectively in modifying the early inflammatory phase and prevent long term neuronal damage and disability progression. Two pivotal phase III trials in RRMS have shown that ocrelizumab is more efficacious in reducing the risk of disability progression than subcutaneous IFNβ-1a [6]. However, the study population in these two pivotal trials did not specifically include early RRMS patients naïve to previous disease modifying therapy. This gap is closed by the prospective open label, single arm MA30143 study. Endpoints of the main study include clinical, MRI and safety parameters but no immunological parameters. It is of particular value to explore immunological consequences of ocrelizumab in early, treatment naïve patients for two major reasons. First, immunological dysregulation is evident in the periphery and plays a role in disease pathophysiology particularly in early RRMS [5, 7]. Second, the immune system has not been modified before in these patients by other immunemodulatory treatments that could bias the natural immunological changes induced by ocrelizumab treatment.

1.2 BENEFIT-RISK ASSESSMENT

The results of this substudy are expected to yield a deeper understanding of ocrelizumab's immunological mechanisms. Given the high potential to provide important cues to individual treatment response and risk-benefit ratio, a minimal added risk due to additional blood samplings occurring the substudy is regarded justified by the sponsor.

2. OBJECTIVES AND ENDPOINTS

The MA30143 (ENSEMBLE) immune substudy will investigate immunological changes associated with Ocrelizumab treatment in a treatment naïve, early stage RRMS population. During the OPERA trials the quantitative evolution of major lymphocyte subsets and NK cells over the study treatment was investigated and correlated with severe infections CTCAE grade III and IV, and herpes and opportunistic infections. The MA30143 immune substudy intends to gain additional insights by observing a broader panel of immune cell types and their functional properties under ocrelizumab treatment. In-depth characterization will be achieved by multicolor flow cytometry, in vitro cell culture and deep sequencing. This multiparametric exploration of the immune system is powerful to reflect its overall functional state which will be measured before, during and post ocrelizumab therapy as well as upon B cell repletion. Individual immune parameters will be correlated with clinical and/or subclinical changes assessed by neurological markers in the main study MA30143.

This explorative study can help to identify immune parameters and biomarkers beneficially influenced by ocrelizumab therapy. Particular beneficial effects on MS immune pathophysiology in the context of B cell depletion can be envisioned as follows:

- Decreased frequencies of proinflammatory immune cell subsets relative to regulatory immune cell subsets
- Decrease of proinflammatory cytokine production by immune effector cells
- Decrease of surface activation marker expression on immune cells
- Mitigation of clonal B and T cell expansion under therapy
- Preserved immune receptor repertoire under B cell depletion and upon B cell reconstitution
- Reversibility of parameters after therapy discontinuation and B cell repletion

2.1 ENDPOINTS - BASIC ANALYSIS

The main endpoint of the MA30143 immune substudy is the quantitative change in circulating immune cell subsets, measured relative to baseline (pre-infusion) at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*. These analyses will be performed in all evaluable patients included in the substudy. Specific parameters are outlined in Table 1.

Table 1 – Basic Analysis: Endpoints and Parameters

Main Endpoint Frequencies of peripheral blood mononuclear cells relative to baseline at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab.*		
Parameter	**Markers**	**Method**
Frequencies of circulating B cells • Naïve B cells • Memory B cells • Marginal zone like B cells • Class switch memory B cells • Unusual B cells • Transitional B cells • Regulatory B cells	CD19, CD20, CD21, CD23, CD24, CD27, CD38, CD80, IgD, IgM	Flow cytometry
Frequencies of circulating T cells • CD4/CD8 T cells • Naïve T cells • Effector T cells • Memory T cells • Regulatory T cells • T helper cell subsets T_H1, T_H2, T_H17 • T follicular helper cells	CD3, CD4, CD8, CD25, CD27, CD39, CD45RA/RO, CD56, CD62L, CD127, CD146, CD161, CD183 CD194, CD195, CD196, CTLA-4 FoxP3, IL-17, IFN-gamma, IL-4, HELIOS	Flow cytometry

Frequencies of circulating NK cells • CD56bright • CD56dim Natural killer T cells	CD3, CD16, CD25, CD56, CD69, CD122, CD244, CD336 NKG2A, NKG2D	Flow cytometry
Frequencies of circulating antigen presenting cells • Myeloid dendritic cells • Plasmacytoid dendritic cells • Monocytes	CD1c, CD11c, CD14, CD16, CD25, CD86, CD141, CD303 (BDCA-2), HLA-DR	Flow cytometry

2.2 ENDPOINTS - EXTENDED ANALYSIS

Endpoints of the extended analysis comprise the functional characterization of immune cell subsets and the characterization of the B and T cell receptor repertoire under ocrelizumab therapy relative to baseline. These comprehensive assessments will be exclusively performed in the first 30 enrolled patients. The endpoints are listed in Table 2.

Table 2 – Extended Analysis: Endpoints

Endpoint	Markers	Method
Expression level of activation markers in peripheral blood T cells relative to baseline at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*	CD25, CD69, HLA-DR	Flow cytometry, quantification by mean fluorescence intensity
Relative and absolute change from baseline of cytokine concentration_at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*	GM-CSF, IFN-γ, IL-6, IL-10, IL-17, IL-23, TGF-beta 1	Cytokine bead array/ELISA from sera
Genetic B cell receptor/antibody clonal diversity relative to baseline at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*	number of total and unique clones, entropy and clonality	Deep immune sequencing
Genetic T cell receptor clonal diversity relative to baseline at *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*	number of total and unique clones, entropy and clonality	Deep immune sequencing

2.3 ASSOCIATIONS

Associations of immunological and clinical/safety parameters outlined in Table 3 will be performed on maximal numbers of patients according to availability of the respective analysis.

Table 3 Correlations with Parameters from the Main Study

Data from the main study as outlined below will be used for correlations with various immune parameters (to be determined in the substudy statistical analysis plan)

Clinical

- Time to onset of confirmed disability progression (CDP) sustained for at least 24 weeks and 48 weeks
- Proportion of patients who have confirmed disability improvement (CDI), CDP or stable disability (i.e. neither CDI nor CDP) assessed annually for at least 24 weeks and 48 weeks
- Change from baseline in Expanded Disability Status Scale (EDSS) score over the course of the study
- Time to first MA30143 protocol-defined event of disease activity
- Time to first relapse
- Annualized relapse rate
- Proportion of patient relapse free by week 48, 96, 144 and 192
- Proportion of patients with no evidence of protocol-defined disease activity (NEDA) over week 96, week 144 and week 192 and per epoch
- Proportion of patients with no evidence of progression (NEP)
- Proportion of patients with no evidence of progression sustained for at least 24 weeks and no active disease (NEPAD
- Change from baseline of Multiple Sclerosis Functional Composite (MSFC) and its composites (T25FW, 9HP, and Paced Auditory Serial Addition Test [PASAT]) over time

MRI

- Total number of T1 Gd-enhancing lesions as detected by brain MRI over time
- Total number of new and/or enlarging T2 lesion as detected by brain MRI over time
- Total number of fluid-attenuated inversion-recovery (FLAIR) lesion counts as detected by brain MRI over time
- Percentage change in brain volume as detected by brain MRI over time

Safety

- serious infections CTCAE grade III or IV
- herpes
- opportunistic infections

3 SUBSTUDY DESIGN

3.1 DESCRIPTION OF THE SUBSTUDY

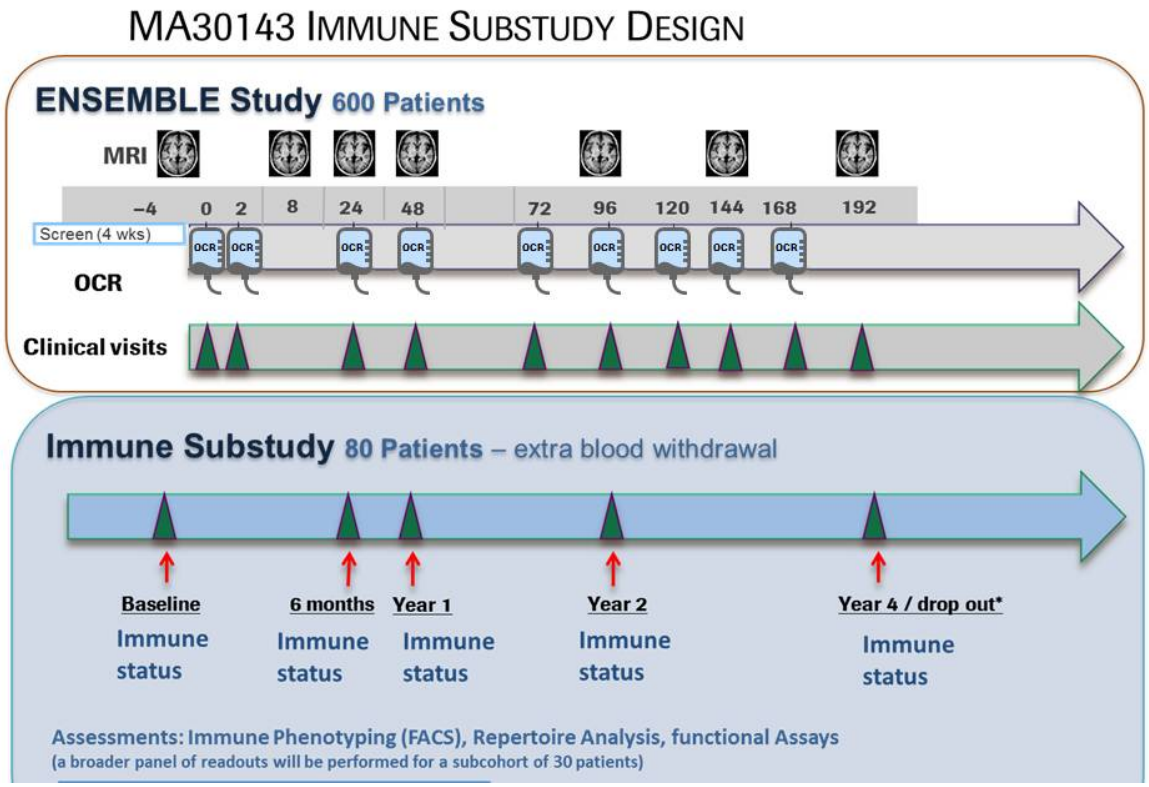
This study is designed as a substudy to the MA30143 prospective, multicenter, open-label and single-arm effectiveness and safety study on ocrelizumab in patients with early stage RRMS. By an in-depth investigation of repopulation dynamics and qualitative changes this substudy aims to understand the consequences of B cell depletion for immune regulatory networks in early stages of MS. The study will utilize the deep immune profiling platform with standardized biosample acquisition, storage, processing and analysis established at the Münster University Hospital, department of Neurology.

Approximately 80 patients, who fulfil eligibility criteria, will be included in this substudy. These will be recruited from approximately 40 sites in Germany and other selected countries. Blood and serum samples will be collected, processed and stored during the 192 week treatment period and the 48 week follow-period of the MA30143 trial (overall storage of samples for up to 5 years after end of study). Clinical and radiological parameters will be derived from the MA30143 trial and correlated with the immunological findings of the substudy. This shall provide cues to immune signatures of immune cell depletion and repopulation associated with parameters of treatment response (clinical and radiological) or safety issues. The Sponsor expects a deeper understanding of ocrelizumab's immunological effects to potentially improve patient selection and guidance and therefore the individual benefit-risk ratio.

Patients giving their consent to participate in this substudy will be asked to provide 6 x 9 mL EDTA blood and 1 x 9 ml serum samples (total blood volume of 63 ml) at baseline, *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab*. Additional samples (6 x *9* mL EDTA blood and 1 x *9* mL serum samples [total blood volume of *63* mL]) will be collected, wherever possible, in cases of relapse, de novo vaccination or severe infection. Samples will be collected at the individual centers. After performing a differential blood count on site, samples will be immediately shipped to Münster University Hospital, where all samples will be further processed and analyzed.

3.2 OVERVIEW OF STUDY DESIGN

Figure 1 - Overview of the Study Procedures



**For dropouts, a measurement 48 weeks after the last infusion of ocrelizumab will be performed to assess immune status during repletion.*

Table 4 – Visit Scheme

	Screening	Treatment Period					*Safety* Follow-up	Unscheduled Visit
Visit # (Main Study)	1	2	5	6	8	12	Ad-hoc	Ad-hoc
Visit # (Substudy)	1	2	3	4	5	6	Ad-hoc	Ad-hoc
Week	-4 to -1	1	24	48	96	192	*48 weeks after last infusion of ocrelizumab*	
Informed consent	X							
Mandatory blood samples[a]		X	X	X	X	X	X	
Informed consent for additional blood samples								X
Additional blood samples in cases of								X

relapse, de novo vaccination or severe infection[b]								

[a] 6 x 9 mL EDTA blood and 1 x 9 mL serum samples (total blood volume of 63 mL) at baseline, *week 24, week 48, week 96, week 192/or early treatment discontinuation visit and at 48 weeks after the last infusion of ocrelizumab.*
[b] 6 x *9* mL EDTA blood and 1 x *9* mL serum samples (total blood volume of *63* mL).

3.3 SCREENING, TREATMENT PERIOD, FOLLOW UP PERIOD

Screening is performed according to procedures defined in the main study protocol. Patients need to enter the substudy before receiving the first dose of ocrelizumab. Treatment period, criteria for re-treatment and follow up period are defined in the main study protocol. *P*atients who prematurely withdraw or finish treatment period will additionally be assessed *48 weeks* after *the last infusion of ocrelizumab.*

3.4 PLANNED TOTAL SAMPLE SIZE

This substudy will enroll approximately 80 patients. Please refer to the Section 6.1 for more details.

3.5 END OF SUBSTUDY AND LENGTH OF SUBSTUDY

Patients will remain enrolled in the substudy as long as in the main study MA30143, if consent is not prematurely withdrawn. Timelines are aligned to the main study. The end of the study treatment period is defined in the main study protocol. The substudy end is defined as the last patient last visit *in the Safety Follow-up period or last patient Week 192 visit, whichever occurs later.*

Total length of the parent study, from screening of the first patient to the end of the study, is expected to be approximately *356* weeks (~7 years). This includes an enrolment period of 116 weeks.

3.6 CENTERS

Sites selected for the main study and located in Germany and other selected countries will be eligible to participate in this substudy. Approximately 40 sites are envisaged to participate in the substudy.

4 MATERIALS AND METHODS

4.1 PATIENTS

Patients with early stage RRMS who fulfill eligibility criteria for the Phase IIIb study (MA30143) and the eligibility criteria outlined in the following inclusion and exclusion sections of this substudy can be enrolled into the substudy. Up to 80 patients will be enrolled in the substudy.

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for substudy entry:

- Enrolled in the Phase IIIb study MA30143
- Signed Informed Consent Form for the MA30143 Immune Substudy
- Able to comply with the substudy protocol, in the investigator's judgment.

4.1.2 Exclusion Criteria

There are no exclusion criteria beyond those listed in the main protocol of the MA30143 study.

4.2 SUBSTUDY ASSESSMENTS

4.2.1 Procedure for enrolment of eligible patients

All patients eligible for the main study are also eligible to enter the substudy, if desired.

Patients must sign and date the most current Institutional Review Board/Institutional Ethics Committee's (IRB/IEC) approved written informed consent form for the main study in which they are participating (MA30143) and a separate informed consent form for the substudy before any substudy-specific assessments or procedures are performed.

4.2.2 Sample Collection and visits assessments

Visits for this substudy will take place as a part of the main study visits.

Patients who have enrolled in the main study and enrolled in this optional research substudy will have additional substudy blood specimens collected at each timepoint as outlined in the schedule of assessments. Seven samples of 9 mL blood will be collected (63 mL). Additional samples (6 x *9* mL EDTA blood and 1 x *9* mL serum samples [total blood volume of *63* mL]) will be collected, wherever possible, in cases of relapse, de novo vaccination or severe infection. Samples will be collected, processed at participating sites and immediately shipped to the Münster University Hospital (UKM) where experiments will be performed. Leftovers of processed specimens, which will consist of frozen cells, will be retained for a maximum of 5 years (for confirmation of results, if appropriate). Those samples will be destroyed once the study report of the substudy has been finalized.

4.3 PATIENT, STUDY, AND SITE DISCONTINUATION

4.3.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the substudy at any time for any reason. Patient's withdrawal from the substudy does not constitute a withdrawal from the main study. Patients withdrawal from main study and/or substudy does not, by itself constitute withdrawal of specimens already collected for the substudy. Consent to this immune substudy may be withdrawn at any time and collected samples destroyed, by contacting

the sponsor, which will ask the investigator to destroy the samples. No replacement for patients who withdraw from the substudy is planned.

4.3.2 Study and Site Discontinuation

The Sponsor has the right to terminate the substudy at any time. The same clauses apply for the substudy as stated in the parent study protocol, Section 4.7.3. Substudy discontinuation does not affect parent study continuation.

5 ASSESSMENT OF SAFETY

5.1 SAFETY ASSESSEMENT

Adverse events related to the substudy procedure will be collected throughout the substudy and reported as per main study. Other adverse events related to disease, medication, or other main study procedures should be reported as outlined in the Safety Assessment and/or Safety Instructions and Guidance sections of the main study protocol (MA30143).

Blood draw may have procedural adverse events such as minor discomfort, lightheadedness, or bruising at the draw site, or in very rare cases, infection. If any AE occurs in regards to the procedure for this substudy sample, it should be reported according to the substudy protocol instructions in the guidance in Section 5.2 below.

5.2 SAFETY INSTRUCTIONS AND GUIDANCE

Safety measures regarding the study medication of the Phase III trials are not part of this substudy, and are detailed in the respective main protocols (MA30143).

5.2.1 Reporting of Adverse Events

If an adverse event specifically related to the substudy procedure occurs, it will be recorded in the e-CRF and documented in the study report and/or substudy report.

5.2.2 Reporting of Serious Adverse Events

If a serious adverse event specifically related to the substudy procedure occurs, the event should be immediately reported to the Sponsor, it will be recorded in the e-CRF and documented in the study report and/or substudy report.)

5.2.3 Emergency Medical Contacts

Refer to Section 5.4.1 of main protocol.

6 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The number of patients expected to participate in this substudy is up to 80. No formal sample size determination was performed. The proposed number of patients is considered appropriate for this exploratory study and is consistent with other similarly conducted

studies in the field (TERY-DYNAMIC Study Clinical trials.gov NCT01863888, Neurology April 5, 2016 vol. 86 no. 16 Suppl- P5.282).

6.2 OUTLINE OF ANALYSES

The results of this substudy are intended to be hypothesis-generating. Data generated as part of this substudy will be presented in a clinical study report separate from that of the parent study.

This is an outline of the main analyses planned for this substudy. More details will be provided in the substudy Statistical Analysis Plan (SAP), which may include additional exploratory analyses not explicitly mentioned in this section.

Analysis populations: the main analysis of this substudy will include all evaluable patients part of the ITT population of the parent study eligible for this substudy.

The analysis will be primarily descriptive. Where appropriate, 95% confidence intervals for point estimates will be calculated and interpreted in an exploratory manner.

Correlations between immunological markers and clinical outcome will be assessed. T cell repertoire analyses will be performed on samples of the first 30 enrolled patients.

Relationship between any CD4+ or CD8+ T cell markers (or any immunological marker at baseline, 24 weeks or 48 weeks of ocrelizumab treatment) and core study efficacy and safety endpoints will be assessed using a regression model to evaluate biomarkers as predictive factors of efficacy or safety endpoints.

6.3 INTERIM ANALYSIS

Exploratory analyses of selected endpoints will be performed during the course of the study, for example, after all patients have completed the first 48 weeks of the treatment phase and the necessary data are available. As no confirmatory statistical tests will be conducted, no formal control to the type-I error rate is needed.

7 DATA COLLECTION AND MANAGEMENT

The overall procedures for quality assurance of clinical study data are described in the Sponsor's (or designee's) Standard Operational Procedures.

The central laboratory for the substudy (Münster University Hospital) will be responsible for data management of this substudy, including quality checking of the data. In event of discrepant data, the Muenster University Hospital will request data clarifications from the site which will be revolved via their capture system.

The sponsor will perform oversight of the data management of this study, including approval of the data management plans and specifications at Münster University Hospital. Sponsor's standard procedures will be used to handle and process the electronic transfer

of these data. The clean data will be transferred to the Sponsor for analysis of the correlations with the clinical or subclinical efficacy and safety profile of the patients included in the substudy.

eCRFs and correction documentation will be maintained in the EDC system's audit trail (for eCRF data – e.g. informed consent, withdrawal of consent, sample collection dates). System backups for data stored at the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Substudy data will be recorded via the instrument used for data acquisition and for most experiments will be processed by Münster University Hospital to generate key data. These non eCRF data will be handled using the Sponsors standard procedures to handle and process these data.

Source data documentation

The Investigators shall supply the Sponsor on request with any required background data from the substudy documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

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.

Retention of records

Records and documents pertaining to the conduct of this substudy, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Use of data from the main study

If patients remain enrolled in the main study beyond the end of the substudy, data collected from the main study may continue to be used for analysis with data generated in the substudy.

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APPENDIX 10
Ocrelizumab Shorter Infusion Substudy Protocol

TITLE:	**A SUBSTUDY TO EVALUATE THE SAFETY OF A SHORTER INFUSION OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS** ASSOCIATED WITH MA30143 CORE STUDY
PROTOCOL NUMBER:	MA30143 shorter infusion substudy
VERSION NUMBER:	4.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

OCRELIZUMAB SHORTER INFUSION SUBSTUDY PROTOCOL ACCEPTANCE FORM

TITLE:	**A SUBSTUDY TO EVALUATE THE SAFETY OF A SHORTER INFUSION OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS** ASSOCIATED WITH MA30143 CORE STUDY
PROTOCOL NUMBER:	MA30143 shorter infusion substudy
VERSION NUMBER:	4.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature | Date

Co-Investigator's Name (print)

Co-Investigator's Signature | Date

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

OCRELIZUMAB SHORTER INFUSION SUBSTUDY PROTOCOL SYNOPSIS

TITLE:	**A SUBSTUDY TO EVALUATE THE SAFETY OF A SHORTER INFUSION OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS** ASSOCIATED WITH MA30143 CORE STUDY
PROTOCOL NUMBER:	MA30143 shorter infusion substudy
VERSION NUMBER:	4.0
EUDRACT NUMBER:	2016-002937-31
IND NUMBER:	100,593
TEST PRODUCT:	Ocrelizumab, RO4964913
PHASE:	Phase IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This substudy will evaluate the safety of a shorter infusion of ocrelizumab in a subgroup of patients with early stage relapsing remitting multiple sclerosis (RRMS) enrolled in the main MA30143 study. Specific objectives and corresponding endpoints for the substudy are outlined in the following table.

Objectives	Corresponding endpoints
Primary objective	
• To assess the proportion of patients with infusion-related reactions (IRRs) following shorter duration infusions of ocrelizumab as compared to conventional infusions in the study population	• Proportion of patients with IRRs occurring during or within 24 hours following the first infusion after randomization to the shorter infusion substudy
Secondary objectives	
• To evaluate the IRR of ocrelizumab in the study population	• Proportion of patients with IRR overall and by dose at randomization • Severity of IRRs • Symptoms of IRRs • IRRs leading to treatment discontinuation
Exploratory objective	
• To further evaluate the IRR of ocrelizumab in the study population	• Proportion of patients with IRRs and serious IRRs • Number of IRRs and serious IRRs • Proportion of patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 (severe) IRRs • Number of IRR with CTCAE grade 3 or 4 (severe) IRRs Analysis will be conducted for IRRs overall and separately during and within 24 hours following for each infusion number after randomization

Substudy Design

This is a prospective, multicenter, randomized, double-blind, controlled, parallel arm substudy evaluating the safety of a shorter duration infusion of ocrelizumab in a subgroup of patients with early stage RMS enrolled in the main MA30143 study. We expect approximately 700 patients to be enrolled in this substudy: expected approximately 150 patients currently participating in the main study, and approximately 550 newly enrolled patients, who will receive the randomized infusion at the second dose. Based on the current recruitment status of the main study, all patients are expected to have received Dose 2, hence new patients are needed to be recruited in order to assess the IRR rate of the shorter infusion at Dose 2. The primary endpoint is the proportion of patients with IRR related to the first infusion after randomization into the substudy. Ocrelizumab dose and schedule remains unchanged in this substudy.

After providing written informed consent, patients will enter a screening period (up to 4-weeks) to be evaluated for eligibility. The patients currently enrolled in the main study can participate in the substudy if they are eligible and provide the written informed consent.

For the additional patients, the first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) as per the main study protocol. At week 24 visit, patients eligible to take part in this substudy will be randomized into the following 2 groups in a 1:1 ratio stratified by region (United States [US], Canada, Australia versus Rest of the World [ROW]).

- One Group: patients will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the study duration (as in the main MA30143 study)
- Other Group: patients will receive a shorter duration infusion of 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour) every 24 weeks for the remainder of the study duration.

Patients already enrolled in the main study will be randomized into the above 2 groups at the next main study visit. The randomization will be stratified by dose at which the patient is randomized and region.

An interim analysis (IA) will be performed when approximately 400 patients will be randomized and dosed.

In this substudy the actual infusion rate for each group is blinded. An independent Data Monitoring Committee (iDMC) will examine unblinded safety data at regular intervals until the primary analysis is performed, as described in the iDMC charter.

The interim analysis became the primary analysis based on the recommendations of the Sponsor internal data review board (DRB), and these data have been submitted to the Health Authorities. As per the iDMC charter, the iDMC is no longer operating; the last independent data review meeting was held on 6th November 2019 and the close-out meeting was held on 22nd January 2020.

In accordance with the statistical analysis plan (SAP), the Roche internal study management team was unblinded to patients included in the primary analysis but remained blinded to patients not included in the primary analysis until all patients have reached their primary endpoint (IRRs at the first randomized dose) and data have been cleaned (on 14 February 2020). After the unblinding of this substudy, patients will continue under the main study protocol.

Number of Patients

Approximately 700 patients are expected to participate in this substudy overall:

- approximately 550 additional patients will be recruited in the main MA30143 study
- approximately 150 patients are expected to be represented by patients currently participating in the main study who consent to be included in this sub-study.

Target Population

Patients with early stage RRMS who fulfil eligibility criteria for the main study (MA30143) and the eligibility criteria outlined below can be enrolled into the substudy.

Inclusion Criteria

Patients must meet the following criteria to be eligible for substudy entry:

- Enrolled in the Phase IIIb study MA30143 (main study)
- Signed Informed Consent Form for this substudy
- Ability to comply with the substudy protocol, in the investigator's judgment.

Exclusion Criteria

- Any previous serious IRR experienced with ocrelizumab treatment.

End of Substudy

The protocol amendment (version 8.0) marks the completion of the shorter infusion substudy and patients will continue under the main study protocol.

Length of Substudy

The total length of the substudy will be dependent on the time of approval of the substudy in each country/site.

Investigational Medicinal Products

Test Product (Investigational Drug)

For the additional patients, the first dose of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15). At week 24 visit, patients will be randomized into 2 groups (patients already enrolled in the main study will be randomized into these 2 groups at the next main study visit), One Group will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the study duration and the other Group will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour) every 24 weeks for the remainder of the study duration.

Non-Investigational Medicinal Products

Pre-medicate with 100 mg of methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes prior to each ocrelizumab infusion and an antihistaminic drug (e.g., diphenhydramine) approximately 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of IRRs. The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

Statistical Methods

Primary Analysis

The primary analysis will be based on the intent-to-treat (ITT) population. The proportion of patients with IRRs in the two randomized groups will be presented together with 95% confidence

interval (CI). Supportive analyses based on per-protocol (PP) and safety population will be performed. The difference between the proportions in two arms will be presented with its 95% CI. A stratified analysis will also be performed, and the details will be specified in the SAP.

Determination of Sample Size

Regarding currently enrolled patients, we assume that approximately 40 and 110 will receive the randomized treatment at Dose 3 or at Dose 4 or at subsequent dose, respectively. In addition, since no currently enrolled patients will receive shorter infusion at Dose 2, we plan to include approximately 550 new patients, of which approximately 500 are expected to receive the randomized treatment at Dose 2 and be evaluable for the primary analysis. In total, approximately 650 patients are expected to be randomized into two groups and be evaluable for the primary analysis.

The different IRR rates at Dose 2, 3 or 4 or at subsequent dose are considered in the calculation of the pooled IRR rate. In the Opera studies (WA21092 and WA21093), 13.7%, 9.6% and 7.8% of patients had at least one IRR at Dose 2, 3 and 4, respectively, which leads to an expected pooled IRR rate of approximately 12.4% excluding Dose 1 for this study. Therefore, we assume an observed IRR rate in the conventional infusion group of 12.4% excluding Dose 1.

Based on the assumption that the IRR rate in control group is 12.4%, a sample size of 650 patients will provide sufficient precision around the IRR rates for this substudy.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
DRB	Data Review Board
IA	Interim Analysis
iDCC	Independent Data Coordinating Center
iDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IRR	Infusion-related reaction
ITT	Intent-to-treat
IxRS	Interactive voice/Web response system
MS	Multiple sclerosis
PP	Per protocol
RMS	Relapsing multiple sclerosis
ROW	Rest of the world
RRMS	Relapsing remitting multiple sclerosis
SAP	Statistical analysis plan
SD	Standard deviation
US	United States

1. BACKGROUND

1.1 RATIONALE FOR THE SUBSTUDY

Ocrelizumab is administered by intravenous infusion as a 600 mg dose every 6 months. The first ocrelizumab dose of 600 mg is always administered as a divided dose (2 x 300 mg infusions administered 14 days apart) to help reduce the incidence of infusion-related reactions (IRRs) which is highest upon the first infusion of ocrelizumab. The incidence and severity of IRRs is also higher upon the first infusion of all other B-cell depleting agents. The subsequent doses of ocrelizumab are administered as a single 600 mg infusion, with a minimum interval of 5 months to be maintained between each dose of ocrelizumab.

IRRs are among the most frequent adverse events associated with ocrelizumab treatment. During the Phase III relapsing multiple sclerosis (RMS) controlled treatment period, the incidence of IRRs in patients receiving ocrelizumab was highest during the first infusion (Dose 1, Infusion 1; 27.5% of RMS OPERA I and II [WA21092 and WA21093] patients pooled), and with subsequent dosing IRRs occurred with decreasing incidence. After the first dose, the incidence (RMS OPERA I and II pooled: 4.7% to 13.7% of patients), severity (Grade 1 or 2; RMS OPERA I and II pooled: 92.6% of patients) and symptoms (in >= 10% of RMS patients with IRRs: pruritus, rash, throat irritation and flushing) of IRRs were similar in both studies.

A preliminary analysis was performed on an ad-hoc data cut (06-April-2018) in the main study (ENSEMBLE) including 675 patients who had received the first infusion of dose 1 and 172 who had received dose 2 at week 24. The proportions of patients with IRRs were 28.7% and 12.2% at dose 1 and dose 2, respectively, which were similar to the rates of 27.5% and 13.5% observed in OPERA I and II pooled.

To reduce the frequency and severity of IRR, patients are pre-medicated with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion, and with an antihistamine (e.g. diphenhydramine) approximately 60 minutes before each infusion. In RMS patients, during the Phase III controlled treatment period, IRRs were also well managed by slowing or interrupting infusions. In 78% of the IRR events, symptomatic therapy for the management of IRR symptoms was needed in addition to the slowing down or interruption of the infusion to manage the IRRs. For 22% of the IRR events, no additional intervention was necessary and infusion adjustments were the only intervention which led to a resolution of the IRR. Therefore, IRRs were not considered as a treatment limiting factor.

The aim of this substudy investigation is to determine differences in IRR rate with acceleration of the ocrelizumab infusion. Infusions with a faster infusion rate can increase the rate of IRRs, and therefore the safety of a faster infusion with ocrelizumab will be assessed in this study. Results of a previous study of rituximab in patients with rheumatoid arthritis (RATE-RA study) showed that there was no increase in the rate or

severity of IRRs with a shorter (over 2.0 hours) infusion of rituximab as compared to the conventional (over 4.25 hours) infusion (Pritchard et al. 2014), based on historical control numbers.

Currently, single infusions of 600 mg ocrelizumab are initiated at a rate of 40 mL/hour. In the absence of IRRs, the rate is increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour with a total estimated infusion time of approximately 3.5 hours. With this conventional infusion, the total observation time for the patient, including the administration of premedication is at least 5.5 hours (this can be prolonged in case infusion is slowed down): 0.5 - 1 hour for premedication and set-up of the infusion; 3.5-hour infusion of ocrelizumab; 1-hour post infusion observation.

A shorter 2-hour infusion would allow for an overall reduction of the ocrelizumab administration to about 3.5 to 4 hours in total (including premedication – 0.5 to 1 hour, drug infusion – 2 hours and observation time – 1 hour) [Please refer to Table 1 for a comparison of the infusion rate and time for the conventional and shorter infusion of ocrelizumab]. The proposed shortening of the infusion time, if assessed in this substudy to be as safe as the conventional infusion, would significantly reduce both the patient burden (i.e. less time taken for treatment administration and faster return to daily activities) and the burden of patient management for the nursing staff (e.g. such as to allow centers the possibility of offering morning/afternoon appointments or the scheduling of two patients in a day rather than one).

Table 1 Comparison of the infusion rate and time for conventional and shorter infusion of 600 mg of ocrelizumab

Infusion type	Infusion rate mL/hr	Time required for infusion			
		Time for premedication and set-up	**Infusion time**	**Time for post-infusion observation**	**Total time**
Conventional infusion Group	Initiated at 40mL/hour and increased to maximum of 200mL/hour	0.5 to 1 hour	**3.5 hours**	1 hour	5.5 hours
Shorter infusion Group	Initiated at 100mL/hour and increased to maximum of 300mL/hour	0.5 to 1 hour	**2.0 hours**	1 hour	4 hours

Of note: The exact ocrelizumab administration rate for each group is blinded in this study.

Please refer to Table 3 for further details on the shorter infusion rates of ocrelizumab

1.2 BENEFITS / RISK ASSESSMENT

Changes to the overall benefit/risk ratio of patients treated with ocrelizumab are not expected due to the shorter infusion. Pre-medication as in main study (100 mg intravenous methylprednisolone and antihistaminics) and other infusion adjustments and symptomatic treatment as judged needed by the investigator are maintained for this blinded evaluation.

2. OBJECTIVES AND ENDPOINTS

This substudy will evaluate the safety of a shorter infusion of ocrelizumab in a subgroup of patients with early stage relapsing remitting multiple sclerosis (RRMS) enrolled in the main MA30143 study. Specific objectives and corresponding endpoints for the substudy are outlined in the following table.

Table 2 Objectives and Corresponding Endpoints

Objectives	Corresponding endpoints
Primary objective	
• To assess the proportion of patients with IRRs following shorter duration infusions of ocrelizumab as compared to conventional infusions in the study population	• Proportion of patients with IRRs occurring during or within 24 hours following the first infusion after randomization to the shorter infusion substudy
Secondary objectives	
• To evaluate the IRR of ocrelizumab in the study population	• Proportion of patients with IRR overall and by dose at randomization • Severity of IRRs • Symptoms of IRRs • IRRs leading to treatment discontinuation
Exploratory objectives	
• To further evaluate the IRR of ocrelizumab in the study population	• Proportion of patients with IRRs and serious IRRs • Number of IRRs and serious IRRs • Proportion of patients with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 (severe) IRRs • Number of IRR with CTCAE grade 3 or 4 (severe) IRRs Analysis will be conducted for IRRs overall and separately during and within 24 hours following for each infusion number after randomization

3. STUDY DESIGN

3.1 DESCRIPTION OF THE SUBSTUDY

This is a prospective, multicenter, randomized, double-blind, controlled, parallel arm substudy evaluating the safety of a shorter infusion of ocrelizumab in a subgroup of

patients with early stage RRMS enrolled in the main MA30143 study. Ocrelizumab dose and schedule remains unchanged in this substudy.

Approximately 150 patients currently participating in the main study are expected to be enrolled and approximately 550 additional patients will be enrolled in the main study specifically for the purpose of this substudy. Based on the current recruitment status of the main study, all patients are expected to have received Dose 2, hence new patients are needed to be recruited in order to assess the IRR rate of the shorter infusion at Dose 2.

After providing written informed consent, patients will enter a screening period (up to 4-weeks) to be evaluated for eligibility. The patients currently enrolled in the main study can participate in the substudy if they are eligible and provide the written informed consent.

For the additional patients, the first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) in all the patients as per the main study protocol. At week 24, patients eligible to take part in this substudy will be randomized into the following 2 groups:

- One Group: patients will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the study duration (as in the main MA30143 study)
- Other Group: patients will receive a shorter infusion of 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours, followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour), every 24 weeks for the remainder of the study duration.

Patients already enrolled in the main study will be randomized into the above 2 groups at the next main study visit.

Randomization into the two treatment groups will be in a 1:1 ratio. For the additional patients, randomization will be stratified by region (United States [US], Canada, Australia versus Rest of the World [ROW]). For patients, already enrolled in the main study, randomization will be stratified by dose at which the patient is randomized and region.

The actual infusion rate for each group is blinded – for details on blinding, please refer to Section 4.2 of this substudy protocol.

Patients will be assessed for safety every 24 weeks as described in the Schedule of Assessments presented in Appendix 1 of the main study protocol.

Please see the main protocol Section 3.1.3 for the criteria for re-treatment with ocrelizumab.

Please see the main protocol Section 3.1.4 for the details on the follow-up period.

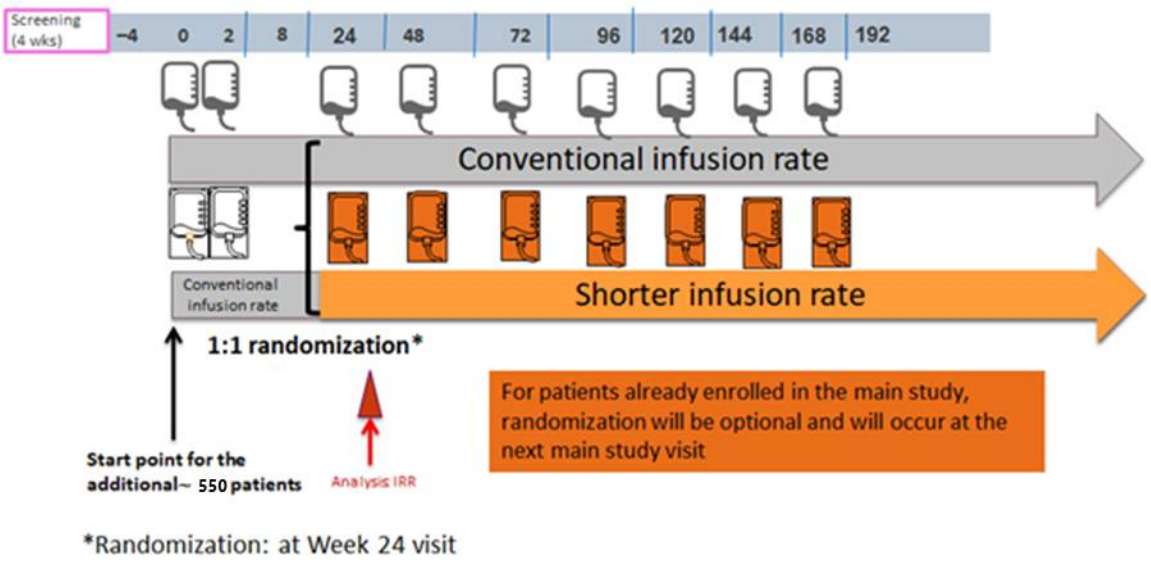
An interim analysis (IA) will be performed when approximately 400 patients will be randomized and dosed (see Section 6.6 of this substudy protocol). An independent Data Monitoring Committee (iDMC) will examine unblinded safety data at regular intervals until the primary analysis is performed, as described in the iDMC charter.

The interim analysis became the primary analysis based on the recommendations of the Sponsor internal Data Review Board (DRB), and these data have been submitted to the Health Authorities. As per the iDMC charter, the iDMC is no longer operating; the last independent data review meeting was held on 6th November 2019 and the close-out meeting was held on 22nd January 2020. In accordance with the statistical analysis plan (SAP), the Roche internal study management team was unblinded to patients included in the primary analysis but remained blinded to patients not included in the primary analysis until all patients have reached their primary endpoint (IRRs at the first randomized dose) and data have been cleaned (on 14 February 2020). After the unblinding of this substudy, patients will continue under the main study protocol.

3.1.1 Overview of study design

Figure 1 presents an overview of the substudy procedures.

Figure 1 Overview of Substudy design



IRR = Infusion-related reaction

3.1.2 Planned Total Sample Size

Approximately 700 patients are expected to participate in this substudy overall.

- approximately 550 additional patients will be recruited into the main MA30143 study
- approximately 150 patients are expected to be represented by patients currently participating in the main study who consent to be included in this substudy.

See Section 6.1 for further details.

3.2 END AND LENGTH OF SUBSTUDY

The protocol amendment (version 8.0) marks the completion of the shorter infusion substudy and patients will continue under the main study protocol.

The total length of the substudy will be dependent on the time of approval of the substudy in each country/site.

3.3 RATIONALE FOR THE SUBSTUDY DESIGN

Please see Section 1.1 (rationale of the substudy)

3.3.1 Rationale for ocrelizumab dose and schedule

Ocrelizumab dose and schedule remains unchanged in this substudy; please see Section 3.3.1 of the main study protocol for the rationale for ocrelizumab dose and schedule. The rationale for accelerating the infusion rate in this substudy is discussed in Section 1.1.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with early stage RRMS who fulfil eligibility criteria for the Phase IIIb study (MA30143) and the eligibility criteria outlined in the following inclusion and exclusion sections of this substudy can be enrolled into the substudy.

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for substudy entry:

- Enrolled in the Phase IIIb study MA30143 (main study)
- Signed Informed Consent Form for this substudy
- Ability to comply with the substudy protocol, in the investigator's judgment.

4.1.2 Exclusion Criteria

- Any previous serious IRRs experienced with ocrelizumab treatment

4.2 METHODS OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized in 2 groups in a 1:1 ratio. For the additional patients, randomization will be stratified by region (US, Canada, Australia versus ROW). For patients, already enrolled in the main study, randomization will be stratified by dose at which the patient is randomized and region. An interactive voice/web response system (IxRS) provider will conduct randomization and hold the treatment assignment code. Blinding of the infusion rates and actual duration of the infusion will be achieved by the following measures:

- The substudy group assignment (randomization) codes will only be visible to the pharmacy personnel preparing the drug infusions and to the unblinded personnel operating the infusion pump (called infusion nurse thereafter).
- Infusions will be pre-loaded and placed into standardized infusion cover bags and placed on an infusion rack, and the actual infusion administration pump will be covered and operated by the unblinded infusion nurse.
- The actual infusion rates and associated activities related to infusion administration will be blinded to the site study team (including the study coordinator and the treating investigator), patient and the Sponsor.
- The standard-length infusion will be administered as described above and in the main study protocol. The shorter infusion will be administered within 2 hours (520 mL infusion volume at the rates as presented in Table 3), followed immediately by administration of a separate 100mL normal saline (0.9 % NaCl) bag without any additional component over the remaining 1.5h with an approximate infusion rate of 60mL/hr. For patients randomized to the standard-length infusion, the infusion nurse will mimic a switch infusion at approximately 2 hours (timing to be adapted depending on the infusion rate adaptation during the first 2 hours). The infusion nurse will check and adjust the infusion rates periodically as needed both for maintaining the correct rates of the infusion and for maintaining of blinding/masking of the two infusion groups (See Figure 2a and b). Adjustments needed for managing IRRs are allowed at any time and should follow the guidance from the main study protocol. Please refer to Section 4.3.2 Dosage, Administration and Compliance for further details on the infusion preparation and administration
- The infusion nurse (unblinded) or the clinical nurse (blinded) will collect patient's vital signs at the time of premedication onwards (see Section 4.5.4 of the main study protocol). Vital signs will be reported in the electronic case report form (eCRF). Blinded treating investigator will evaluate and confirm all IRRs occurring during or within 24 h post-infusion.
- The unblinded information related to the infusion will be entered into the IxRS by the unblinded site staff member. The unblinded site staff members have to keep any data related to the infusion (group allocation, infusion duration and content, etc.) confidential:

  - they must not further communicate these data, neither verbally nor in writing– they will maintain the corresponding files in a locked, access restricted location
- Additional operational measures will be undertaken at local level to ensure the appropriate level of blinding of the personnel involved and the data collected.
- IxRS Service Provider and iDMC members will have access to treatment assignment in order to fulfil their roles during the clinical trial.

Figure 2a Blinding Procedure

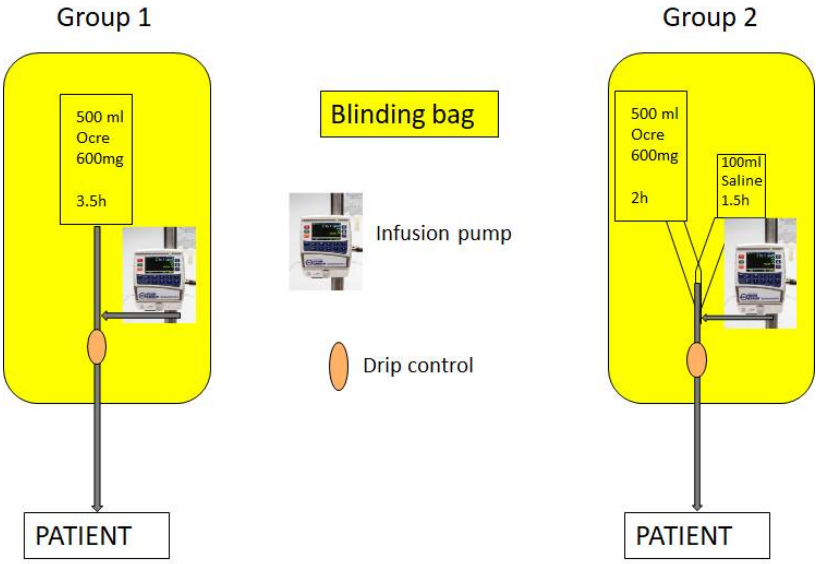
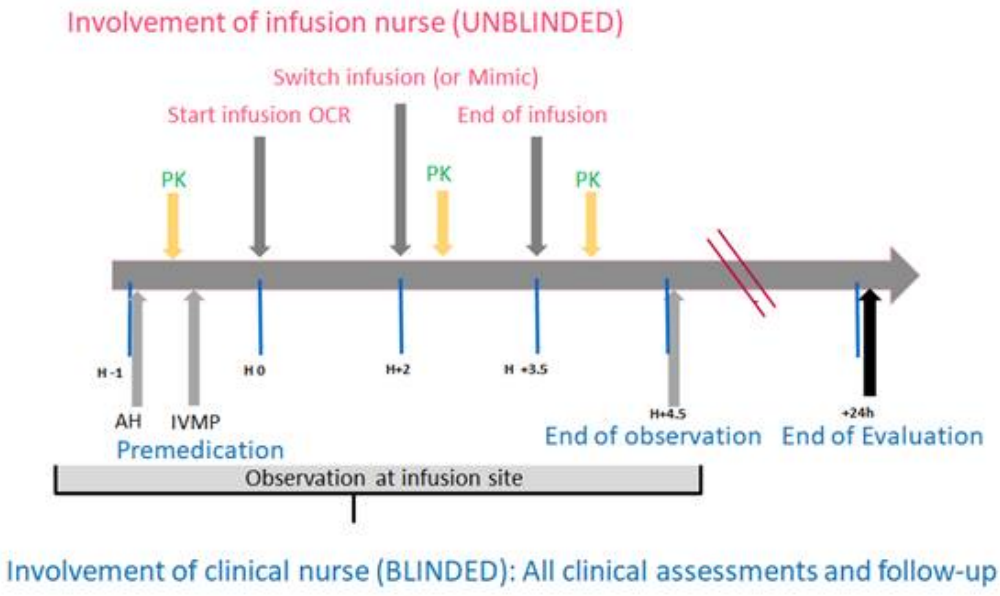


Figure 2b Blinding Procedure



AH = antihistamine; H = hour; IVMP = intravenous methylprednisolone; OCR = ocrelizumab; PK = pharmacokinetic

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

If the investigator wishes to know the patient assignment group in the study for any reason other than a medical emergency, he or she should contact the Medical Monitor directly prior to unblinding. The investigator should document and provide a justification for any non-emergency unblinding. The investigator will be able to break the code by contacting the IxRS.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, Storage and Handling

Please see Section 4.3.1.1 of the main study protocol

4.3.2 Dosage, Administration and Compliance

For the additional patients, the first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15). From Week 24 visit, patients randomized to the conventional infusion will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the study duration and those randomized to the shorter infusion will receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours, followed by an infusion with 100 mL normal saline given as a slow infusion (proposed infusion rate of 60 mL/hr) over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour), given every 24 weeks for the remainder of the study duration. (See also Table 3 for the actual infusion rates to be applied in shorter infusion group)

Table 3 Ocrelizumab infusion rates for Conventional and Shorter Infusion in absence of IRRs (administered in a blinded fashion)

Time in mins	Shorter infusion*			Conventional infusion		
	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
0-15	100	30	30	40	23.18	23.18
16-30	200	60	90			
31-60	250	150	240	85	49.27	72.45
61-90	300	180	420	130	75.36	147.81
91-120	300	180	600	169	98.05	245.86
121 – 215*				200	354.14	600

* After the end of administration of the ocrelizumab infusion bag (520 mL over 2 hours using above rates), there is a change of bags to the 100 mL normal saline one and the continuation of the infusion of 100 mL normal saline at rate 60 mL/hour, for approx.1.5 hours.

For further instructions on shorter infusion as well as for the conventional infusion, please refer to the “Drug Preparation and Blinding Guidelines”.

It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits. Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300 mg dose, approximately 215 minutes (approximately 3.5 hours) for the 600 mg dose for patients randomized to the conventional infusion and approximately 120 minutes (2.0 hours) for the 600 mg dose for patients randomized to the shorter infusion. The exact ocrelizumab administration rate for each group is blinded in this study.

To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone, or equivalent, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion and an antihistaminic drug (e.g., diphenhydramine) approximately 60 minutes before each infusion of ocrelizumab. Additional premedication is recommended (see Section 4.3.3 of the main study protocol).

4.3.3 Prophylactic Treatment

See Section 4.3.3 of the main protocol for details.

4.3.4 Investigational Medicinal Product Accountability

See Section 4.3.4 of the main protocol for details.

4.3.5 Continued Access to Ocrelizumab

See Section 4.3.5 of the main study protocol for the details.

4.4 CONCOMITANT THERAPY

See Section 4.4 of the main protocol for details.

4.5 STUDY ASSESSMENTS

See Section 4.5 of the main study protocol for details of the substudy assessments.

4.5.1 Pharmacokinetic (PK) Sample collection:

Three (3) serum samples will be collected on the first randomized visit.

- First sample will be collected 5-30 minutes prior to the methylprednisolone infusion.
- Second sample will be collected 30 minutes (±10 minutes) after the switch (shorter infusion) or the mimic switch (conventional infusion). To help keep the blind, please collect this sample variably within ±10 minutes of the saline/mimic switch.
- Third sample will be collected 30 minutes (±10 minutes) after completion of the infusion (at the end of ocrelizumab infusion for the conventional infusion or saline infusion for the shorter infusion).

If a PK sample is missed on the first randomized visit, the 3 PK samples should be collected at the next blinded visit.

4.5.2 Infusion Follow-up Telephone contact:

The period of evaluation of the IRRs will be 24 hours after the end of each blinded infusion. A structured telephone interview should be conducted by site personnel on the following working day after the end of each blinded infusion, starting at week 24 to identify and collect information on any possible IRRs or any other changes in the patient's health status, which may have occurred after the discharge.

4.6 TREATMENT, PATIENT, SUBSTUDY AND SITE DISCONTINUATION

4.6.1 Substudy Treatment discontinuation

Reasons for substudy treatment discontinuation are listed in Section 4.7.1 of the main study protocol.

4.6.2 Patient discontinuation from Substudy

Patients have the right to voluntarily withdraw from the substudy at any time for any reason. Patient's withdrawal from the substudy after randomization into Group one or Group two does not constitute a withdrawal from the main trial. No replacement is planned for patients who withdraw.

4.6.3 Substudy Discontinuation

The Sponsor has the right to terminate this substudy at any time. The Sponsor will notify the investigator if the Sponsor decides to discontinue the substudy.

The Sponsor also has the right to terminate the main study at any time. Reasons for termination are listed in Section 4.7.3 of the main study protocol. The Sponsor will notify the investigators if the Sponsor decides to discontinue the main study. Consequently, the substudy could be stopped as well.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for termination are listed in Section 4.7.4 of the main study protocol.

5. ASSESSMENT OF SAFETY

5.1 SAFETY ASSESSMENT

Adverse events related to the substudy will be collected throughout the substudy, according to the procedures outlined in the main study protocol.

5.2 SAFETY INSTRUCTIONS AND GUIDANCE

Safety measures are detailed in the main study protocol.

5.3 REPORTING OF ADVERSE EVENTS

Refer Section 5.4.2 of the main study protocol.

5.4 REPORTING OF SERIOUS ADVERSE EVENTS

Refer Section 5.4.2 of the main study protocol.

5.5 EMERGENCY MEDICAL CONTACTS

As mentioned in the main study protocol, to ensure the safety of study patients an Emergency Medical Call Centre 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 Responsible (listed on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours a day, 7 days a week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.6 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEE

Please refer to Section 5.7 of the main study protocol.

An iDMC will regularly review unblinded IRR data during the study as described in the iDMC charter. iDMC recommendations leading to change of study conduct will be communicated to the health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analyses will be performed using the intent-to-treat (ITT) population. The per-protocol (PP) population and safety population will be used for supportive analyses. The analyses will be performed when all patients have completed the 24-hour observation period after the first randomized infusion. All the analysis will be performed for descriptive purposes and no formal hypothesis testing will be performed.
Detailed specifications will be included in the SAP.

ITT Population

All randomized patients will be included in the ITT population. Patients will be analyzed according to their randomized treatment.

PP Population

The PP population will include all ITT patients without protocol deviations deemed to affect the assessment of the primary endpoint. The list of criteria leading to exclusion from the PP population will be finalized prior to database closure and documented in the SAP. Patients who receive the opposite infusion type from the randomized one will be excluded from the per protocol population.

Safety Population

The safety population will include all randomized patients who received any dose or part of a dose of ocrelizumab. Randomized patients who receive the opposite infusion type from the randomized one will be summarized in the group according to the treatment actually received.

6.1 DETERMINATION OF SAMPLE SIZE

Regarding currently enrolled patients, we assume that approximately 40 and 110 will receive the randomized treatment at Dose 3 or at Dose 4 or at subsequent dose, respectively. In addition, since no currently enrolled patients will receive shorter infusion at Dose 2, we plan to include approximately 550 new patients, of which approximately 500 are expected to receive the randomized treatment at Dose 2 and be evaluable for the primary analysis. In total, approximately 650 patients are expected to be randomized into two groups and be evaluable for the primary analysis.

The different IRR rates at Dose 2, 3 or 4 or at subsequent dose are considered in the calculation of the pooled IRR rate. In the Opera studies (WA21092 and WA21093),

13.7%, 9.6% and 7.8% of patients had at least one IRR at Dose 2, 3 and 4, respectively, which leads to an expected pooled IRR rate of approximately 12.4% excluding Dose 1 for this study. Therefore, we assume an observed IRR rate in the conventional infusion group of 12.4% excluding Dose 1. The 95% confidence intervals (CIs) of the IRR rate difference between shorter and conventional infusion groups as a function of the observed IRR rate in the shorter infusion group are listed in Table 4. The CIs were calculated based on the assumption of Binomial distributed IRR rates, which provide sufficient precision around the IRR rates for this substudy.

Table 4 95% confidence interval of IRR rate difference under different scenarios.

IRR rate in conventional infusion (%)	IRR rate in shorter infusion (%)	Difference in IRR rate (%)	95% CI
12.4	12.4	0	(-5.1, 5.1)
12.4	13.4	1	(-4.2, 6.2)
12.4	14.4	2	(-3.2, 7.2)
12.4	15.4	3	(-2.3, 8.3)
12.4	16.4	4	(-1.4, 9.4)
12.4	17.4	5	(-0.5, 10.5)
12.4	18.4	6	(0.5, 11.5)

IRR = Infusion-related reaction; CI = Confidence interval

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, screening failures, ocrelizumab administration, and discontinuations from the study will be summarized using descriptive statistics (frequency tables for categorical endpoints and mean, median, range, standard, deviation [SD] and 25th-75th quartiles for the continuous endpoints) according to randomized treatment group. Patient disposition and the incidence of treatment discontinuation for different reasons will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics (age, gender, and self-reported race), medical history and neurological examination will be summarized by randomized treatment group. The following will also be summarized: multiple sclerosis (MS) disease history (duration since first MS symptoms, duration of MS since diagnosis, relapses in the past year), and other important variables.

6.4 EFFECTIVENESS ANALYSES

No effectiveness analysis is currently planned for this study.

6.5 SAFETY ANALYSES

The primary endpoint is the proportion of patients with IRRs occurring during or within 24 hours following the first infusion after randomization to the shorter infusion substudy.

The primary analysis will be based on the ITT population. The proportions of patients with IRRs in the two randomized groups will be presented together with 95% confidence interval. Supportive analyses based on the PP and the safety population will be performed. The difference between the proportions in two arms will be presented with its 95% CI. A stratified analysis will also be performed, and the details will be specified in the SAP.

The following IRR-related variables will be summarized:

- Proportion of patients with IRR overall and by dose at randomization
- Severity of IRRs
- Proportion of patients with serious IRRs
- Symptoms of IRRs
- IRRs leading to treatment discontinuation
- Subgroup analyses according to IRR history (for example, patients with/without IRR at any previous dose)

An external iDMC will periodically review safety data up to the primary analysis. Analyses required for the iDMC data review will be performed as described in the iDMC Charter and IDMC data handling plan.

6.6 INTERIM ANALYSIS

An IA for the primary endpoint will be conducted after approximately 400 patients have been randomized and dosed. The data for the IA will be cleaned and signed off by the Principal Investigator or delegate. An iDCC will be responsible for conducting the IA, and study interim results will only be reviewed by the iDMC and a Sponsor internal DRB. Details for the conduct of the IA will be pre-specified in the Sponsor internal DRB charter. In addition, regular safety analyses will be performed by the iDCC and reviewed by the iDMC according to the iDMC charter.

The interim analysis became the primary analysis based on the recommendations of the Sponsor internal DRB and these data have been submitted to the Health Authorities. As per the iDMC charter, the iDMC is no longer operating; the last independent data review meeting was held on 6th November 2019 and the close-out meeting was held on 22nd

January 2020. In accordance with the SAP, the Roche internal study management team was unblinded to patients included in the primary analysis but remained blinded to patients not included in the primary analysis until all patients have reached their primary endpoint (IRRs at the first randomized dose) and data have been cleaned (on 14 February 2020). After the unblinding of this substudy, patients will continue under the main study protocol.

7. DATA COLLECTION AND MANAGEMENT

See Section 7 of the main study protocol for details on data collection and management.

8. ETHICAL CONSIDERATIONS

See Section 8 of the main study protocol for details on ethical considerations

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

See Section 9 of the main study protocol for details on study documentation, monitoring, and administration.

An unblinded CRA will be responsible to monitor the “unblinded” data at the site, thus would identify and react to any errors. An unblinded centralized monitor will be responsible to remotely monitor the "unblinded" data at the study level in order to ensure the overall data consistency and quality.

9.1 INDEPENDENT DATA MONITORING

An iDMC will be employed to monitor and evaluate patient safety until the primary analysis is performed. Monitoring details will be described in the iDMC Charter.

10.REFERENCES

Pritchard CH, Greenwald MW, Kremer JM, et al. Safety of infusing rituximab at a more rapid rate in patients with rheumatoid arthritis: results from the RATE-RA study. BMC Musculoskeletal Disorders 2014;15:177-85.

Appendix 1 to the Shorter Infusion Substudy: Schedule of Assessments

Only assessments specific to the substudy are listed below, please see Appendix 1 of the main study protocol for all other assessments.

Visit	Screening	Treatment Period [a]											Early study treatment discontinuation evaluation	Follow-Up 48 weeks after end of Treatment Period [b]
	1	2 (Baseline)	3	4	5	6	7	8	9	10	11	12		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)	120 (±14 days)	144 (±14 days)	168 (±14 days)	192 (±14 days)		
Informed consent[c]	X													
Randomization [d]					X									
PK of ocrelizumab [e]					X	X*	X*	X*	X*					
Vital signs [f]	X	X	X		X	X	X	X	X	X	X			
Telephone contact 24 hours after each blinded infusion [g]					X	X	X	X	X	X	X			

PK = Pharmacokinetic

[a] The study visits during the treatment period may be spread over more than one day to complete all the assessments before study drug administration.

[b] The follow-up period will begin when the patient discontinues from the study for any reason. Patients who discontinue treatment early should remain in follow-up for 48 weeks following the last infusion of ocrelizumab. Please see Appendix 2 of the main study protocol for the details. Patients who complete the 192 weeks Treatment Period and decide not to continue in a separate long-term extension study, will be followed-up for at least 48 weeks after the end of the Treatment Period.

[c] Written informed consent will be obtained from all patients during screening in order to be eligible for this substudy.

[d] At week 24 visit, all the additional patients will be randomized into 2 groups, one Group will receive 600 mg of ocrelizumab infused over 3.5 hours and the other Group will receive 600 mg ocrelizumab over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in order to mimic the standard-length infusion (3.5 hour) for the rest of the study duration. Patients already enrolled in the main study, will be randomized into 2 groups at the next main study visit.

[e] On infusion visits, three serum samples are collected, one 5-30 minutes prior to the methylprednisolone infusion, the second one 30 minutes (±10 minutes) after the switch (shorter infusion) or the mimic switch (conventional infusion), and the third sample 30 minutes (±10 minutes) after completion of the infusion (at the end of ocrelizumab infusion for the conventional infusion or saline infusion for the shorter infusion). If a PK sample is missed on the first randomized visit, the 3 PK samples should be collected at the next blinded visit.

[f] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion and administration of antihistaminics. In addition, vital signs should be obtained prior to the ocrelizumab/saline infusion, then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. Vital signs will be reported in the eCRF for all the blinded infusions from premedication till patient leaves the infusion site.

[g] The period of evaluation of the IRRs will be 24 hours after the end of each blinded infusion. A structured telephone interview should be conducted by the site personnel on the following working day after the end of each blinded infusion, starting at week 24 to collect information on any possible IRRs or any other changes in the patient's health status, which may have occurred after the discharge.

* For patients who are already enrolled in the main study and only at the first infusion post randomization.