PROTOCOL

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA25046
VERSION NUMBER:	K
TEST COMPOUND:	Ocrelizumab (RO4964913)
STUDY PHASE:	Phase III
EUDRACT NUMBER:	2010-020338-25
IND NUMBER:	100,593
NCT NUMBER:	NCT01194570
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche, Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
20-Nov-2021 01:39:31	[redacted]	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
K	See electronic date stamp on title page.
J	13 July 2020
I	17 December 2019
H	3 August 2018
G	24 September 2017
F	23 March 2016
E	6 February 2015
D	15 June 2012
C	9 April 2012
B	3 March 2011
A	23 June 2010

PROTOCOL AMENDMENT, VERSION K
RATIONALE

Protocol WA25046 (ORATORIO) has been amended to introduce the option of a rollover study (MN43964), into which all ongoing participants can enroll during the course of 2022. As already stated in the current protocol, ocrelizumab treatment via this study is due to finish by December 2022. The Sponsor has now made the decision not to extend this study further and; therefore, this study will end on 31 December 2022. Instead, the new rollover extension study (MN43964) is being set up to ensure that participants of Study WA25046 (together with participants from other Parent studies) can continue their ocrelizumab treatment or safety follow-up as applicable without interruption and allowing for valuable long-term data to continue to be collected.

In addition, a reduction in the safety follow-up period and the incorporation of the risk assessment of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the participant population are implemented through this amendment. Please see below for a summary of the substantive changes to the protocol, along with a rationale for each change:

- To introduce the option for all ongoing participants of Study WA25046 to enroll into a new open-label extension study (MN43964) prior to or following the closure of Study WA25046
- To clarify that participants who discontinue treatment early for any reason and that participants who complete the study treatment period will be followed up for a up to 48 weeks after the last infusion of ocrelizumab. The requirement for continued B cell monitoring for participants whose B cells are not repleted (i.e., returned to baseline levels or the lower limit of normal, whichever is lower) at the end of the safety follow-up period has been removed because no increased safety risk was identified in the ocrelizumab clinical development program following cessation of treatment.
- To clarify that after entering safety follow-up and upon treatment initiation with another disease-modifying therapy (DMT), participants will be discontinued from the safety follow-up and from the study. The rationale for this change is that, given the low numbers of participants in the clinical development program who have switched to alternative DMTs, and data consisting of several different DMTs with various treatment durations, the Sponsor considers that such data would not allow for any meaningful interpretation and it is unlikely that prolonged data collection would facilitate this. Participants who switch to commercial ocrelizumab (OCREVUS®) after entering safety follow-up, will also be discontinued from safety follow-up and the study.
- To incorporate the risk assessment for concomitant use of SARS-CoV-2 vaccines: Section 2.2 has been updated to include the benefit–risk assessment of the concomitant use of SARS-CoV-2 vaccines on the conduct of this study. Based on that assessment, no impact is anticipated on the efficacy and safety in participants enrolled in ocrelizumab clinical trials. The existing information on identified risks,

safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) provided in the study protocol are considered adequate.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA25046
VERSION NUMBER:	K
TEST COMPOUND:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR NAME:	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 of the signed form to the Sponsor or their designee.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**

Study Rationale

This study (WA25046) is a pivotal Phase III clinical trial composed of a blinded treatment period, an open-label extension (OLE) phase, and a safety follow-up period. The blinded treatment period is designed to demonstrate the efficacy and safety of ocrelizumab in primary progressive multiple sclerosis (PPMS) in comparison with placebo. The OLE serves to evaluate long-term safety, tolerability, and efficacy of ocrelizumab treatment in participants with PPMS.
This study is part of a broader, confirmatory clinical development program investigating the safety and efficacy of ocrelizumab in participants with both relapsing multiple sclerosis (RMS) and PPMS. An OLE phase of the Phase II Study WA21493/ACT4422G is ongoing for eligible participants with relapsing-remitting multiple sclerosis (RRMS). There are 3 ongoing Phase III pivotal trials (including the one presented in this protocol), 2 trials in RMS and 1 trial in PPMS.

Objectives

Primary

To investigate the efficacy of ocrelizumab compared with placebo in participants with PPMS, as measured by the time to onset of confirmed disability progression over the treatment period, defined as an increase in Expanded Disability Status Scale (EDSS) that is sustained for at least 12 weeks, based on regularly scheduled visits.
Disability progression is defined as an increase of $\geq$ 1.0-point from the baseline EDSS when the baseline score is 5.5 or less, and $\geq$ 0.5 when the baseline score is more than 5.5, that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication).

Secondary Objectives

The secondary objectives of this study are to evaluate the efficacy and safety of ocrelizumab compared with placebo, as reflected by the following:

- The time to onset of confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 24 weeks, based on regularly scheduled visits
- The change in Timed 25-Foot Walk Test (T25FWT) from baseline to Week 120
- The change in total volume of T2 lesions on magnetic resonance imaging (MRI) scans of the brain from baseline to Week 120
- The percentage change in total brain volume as detected by brain MRI from Week 24–120
- The change in Short Form-36 (SF-36) Health Survey version 2 Physical Component Summary (PCS) score from baseline to Week 120
- To evaluate the safety and tolerability of ocrelizumab 300 mg$\times$2 (over 24-week treatment cycles) compared with placebo in participants with PPMS

Overall Design

This is a Phase III, randomized, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of two 300 mg ocrelizumab IV infusions of separated by 14 days at a scheduled interval of every 24 weeks as compared with placebo in adults with PPMS. Participants will be treated for a minimum of 120 weeks representing at least five 24-week treatment cycles. The study will enroll approximately 630 participants in a 2:1 randomization (ocrelizumab:placebo), globally. Randomization will be performed through an Interactive voice or Web-based response system (IxRS) and will be stratified by region (U.S. vs. Rest of World [ROW]) and age ($\leq$45 vs. $>$45).

This study consists of the following study periods: a screening period, a blinded treatment period, an OLE phase, and a safety follow-up period. The study duration will vary for each participant to maximize the safety and efficacy data collected, as described below.

Screening Period

The screening period lasts up to 4 weeks.

Blinded Treatment Period

All participants will undergo at least 120 weeks of study treatment representing 5 treatment cycles, each of 24 weeks' duration. The study will be unblinded when the last enrolled participant completes at least 120 weeks (5 cycles) of study treatment, provided the total number of confirmed disability progression events is approximately 253 (based on the Sponsor's best estimation after the last participant finishes Week 108 visit), or at the latest when the last randomized participant has been in the blinded treatment period for 3 years.

If the projected number of confirmed disability progression events has not been reached by Week 120 because of slower than anticipated disability progression rates, the treatment period will be extended until approximately 253 confirmed disability progression events have occurred, with additional treatment cycles every 24 weeks, in order to maintain statistical power to detect a treatment difference. Because it is anticipated that it may take 12–18 months to recruit participants, this blinded treatment period may extend to up to 3.5–4 years for the first group of participants enrolled into the study.

If the last participant enrolled discontinues the treatment period before Week 120 or before 3 years of blinded treatment, the date of 120 weeks or 3 years after his/her randomization date will be used.

Randomization (Day 1) will occur only after the participant has met all inclusion and exclusion criteria. For the first treatment cycle and in subsequent treatment cycles of study drug every 24 weeks, participants will be dosed 14 days apart (300 mg ocrelizumab or placebo infusion × 2). All participants will also receive a 100 mg methylprednisolone IV infusion on Day 1 and with each subsequent ocrelizumab or placebo infusion. In participants where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication.

Open-Label Extension Phase

Following database lock of the blinded treatment period, participants should continue to receive blinded treatment until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor.

Upon the disclosure of results and a positive benefit–risk assessment of the use of ocrelizumab therapy, participants who completed the blinded treatment period and who, in the opinion of the investigator, could benefit from treatment may receive open-label ocrelizumab. Unless the Sponsor decides to terminate the ocrelizumab program for multiple sclerosis, the OLE phase will continue as per local regulation. This decision will be based on the change of benefit–risk and safety monitoring. Eligible participants need to provide consent for participation in the OLE phase. Unless *discontinued* early, all participants may continue their treatment with open-label ocrelizumab as per the protocol until 31 December 2022. *All participants must discontinue open-label ocrelizumab treatment within this study before 31 December 2022. However, participants will be offered continuation of ocrelizumab treatment or a safety follow-up period via a rollover study (MN43964, OLERO).*

Participants who start treatment with commercial ocrelizumab *or another DMT* will discontinue from the study completely and will not enter the safety follow-up period.

Participants who are not willing to participate in the OLE phase of the study will enter the safety follow-up period (see below). In the case of a participant who initially declines participation in the OLE phase and subsequently changes their decision, the participant may be deemed eligible to enter the OLE phase up to 24 weeks after the OLE phase begins. This will occur on a case-by-case basis in consultation with the Sponsor.

Participants who consent to participate in the OLE phase will be required to meet the treatment/re-treatment criteria prior to infusion with ocrelizumab. During the OLE phase, all participants will receive dual IV infusions of ocrelizumab 300 mg × 2 for the first cycle. For the

subsequent cycles, participants will continue open-label treatment with a single 600 mg ocrelizumab IV infusion every 24 weeks. Participants who withdraw from the OLE phase will be entered into the safety follow-up period.

Safety Follow-Up Period

The safety follow-up period will begin when the participant completes or discontinues from the blinded treatment period or OLE phase for any reason. Participants should remain in the safety follow-up period for *up to* 48 weeks following the last infusion of study drug/open-label ocrelizumab (as applicable).During the safety follow-up period, participants will be assessed at clinical visits every 12 weeks. Telephone interviews will be performed every 4 weeks *between visits*.

Participants who start commercial ocrelizumab *or another DMT* will be discontinued from the study completely and will not enter or continue in the safety follow-up period.

Because this study will be closed on 31 December 2022, participants already in safety follow-up may complete this study period in the rollover Study MN43964.

It is important to distinguish between "withdrawal from treatment" and "withdrawal from study". Participants who withdraw from treatment should be encouraged to remain in the study for the full duration of the safety follow-up period (*up to* 48 weeks from the last infusion).

Every effort should be made to ensure that participants who withdraw from study treatment complete the safety follow-up period and all related assessments, regardless of whether or not they receive alternative treatment for MS

Number of Participants

Approximately 630 participants will be randomized in 2 groups in a 2:1 ratio. An independent IxRS provider will conduct randomization and hold the treatment assignment code.

Participants will be stratified by region (U.S. vs. ROW) and age (≤45 vs. >45).

There will be no replacement of participants should a participant's treatment be discontinued for any reason.

Study Treatment

During the blinded treatment period, participants will be randomly assigned to either ocrelizumab 300 mg×2 or placebo. The first IV infusion of ocrelizumab or placebo will be administered on study Day 1.

During the OLE phase, all participants will receive 2 IV infusions of 300 mg ocrelizumab separated by 14 days for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab every 24 weeks.

To reduce potential infusion-related reactions, all participants will receive prophylactic treatment with 100 mg methylprednisolone, administered by slow IV infusion, and an oral or IV antihistamine (such as diphenhydramine 50 mg or equivalent dose of alternative).

The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In participants where methylprednisolone is contraindicated, corresponding doses of other IV steroids (e.g., dexamethasone) should be used as premedication.

End of Study

The end of study is now defined as *31 December 2022 or up until the approval of Study MN43964 (OLERO).*

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

The Sponsor has decided to provide the opportunity to all participants to rollover and continue their treatment and/or safety follow-up under the new extension protocol.

Independent Data Monitoring Committee

An independent Data Monitoring Committee is not being used.

1.2 SCHEDULE OF ACTIVITIES

Note: when completing the Week 120 visit, see Table 1. For the Week 122 and all subsequent visits, see Table 2.

Table 1 Schedule of Activities: Screening through the End of Treatment Period

	Screening	Blinded Treatment Period															
Visit	1	2 BL	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	–4 to–1	w1	w2	w12	w24	w26	w36	w48	w50	w60	w72	w74	w84	w96	w98	w108	w120 [a]
Study Day (window in days)	–28 to–1	1	15 (±2)	85 (±4)	169 (±2)	183 (±2)	253 (±4)	337 (±2)	351 (±2)	421 (±4)	505 (±2)	519 (±2)	589 (±4)	673 (±2)	687 (±2)	757 (±4)	841 (±2)
																	
Informed consent [b]	x																
Medical history	x																
Review inclusion/exclusion criteria	x	x															
Physical examination	x	x	x		x	x		x	x		x	x		x	x		x
Vital signs [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12 lead ECG	x	x						x									x
Height	x																
Weight	x																x
Neurological examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EDSS and MSFCS	x	x		x	x		x	x		x	x		x	x		x	x
Adverse events	Only SAEs [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Potential relapses recorded		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1 Schedule of Activities: Screening through the End of Treatment Period (cont.)

	Screening	Blinded Treatment Period															
Visit	1	2 BL	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	–4 to–1	w1	w2	w12	w24	w26	w36	w48	w50	w60	w72	w74	w84	w96	w98	w108	w120 [a]
Study Day (window in days)	–28 to–1	1	15 (±2)	85 (±4)	169 (±2)	183 (±2)	253 (±4)	337 (±2)	351 (±2)	421 (±4)	505 (±2)	519 (±2)	589 (±4)	673 (±2)	687 (±2)	757 (±4)	841 (±2)
																	
MFIS, SF-36, EQ-5D		x						x									x
Telephone interview (every 4w) [e]				x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant treatment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MRI [f]		x			x			x									x
Pregnancy test [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Antibody titers [h]		x															x
RCR (DNA) [i]		x															
RCR (RNA) [j]		x		x	x			x			x			x			x
RCR (Protein) [k]		x		x	x			x			x			x			x
HAHA [l]		x		x	x			x			x			x			x
PK samples [m]		x		x	x			x			x		x	x			x
Clinical genotyping [n]		x															
Protein biomarker sampling [o]		x															
Thyroid function tests	x																

Table 1 Schedule of Activities: Screening through the End of Treatment Period (cont.)

	Screening	Blinded Treatment Period															
Visit	1	2 BL	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	–4 to –1	w1	w2	w12	w24	w26	w36	w48	w50	w60	w72	w74	w84	w96	w98	w108	w120 [a]
Study Day (window in days)	–28 to–1	1	15 (±2)	85 (±4)	169 (±2)	183 (±2)	253 (±4)	337 (±2)	351 (±2)	421 (±4)	505 (±2)	519 (±2)	589 (±4)	673 (±2)	687 (±2)	757 (±4)	841 (±2)
																	
Quantiferon – TB Gold (Germany only)	x																
HIV1 / HIV2 test (Germany only)	x																
FSH [p]	x																
Hepatitis screening [q]	x																
HBV DNA [q]	x			x	x		x	x		x	x		x	x		x	x
RPR	x																
CD4 count	x			x			x			x			x			x	
IgG				x			x			x			x			x	
Total Ig, IgA, IgG, IgM	x				x			x			x			x			x
FACS [r]		x	x	x	x			x			x			x			x
Routine safety laboratory tests [s]	x	x		x	x		x	x		x	x		x	x		x	x
CSF sampling (lumbar puncture) [t]	x																
Plasma/urine banking for JCV [u]		x		x	x		x	x		x	x		x	x		x	x

Table 1 Schedule of Activities: Screening through the End of Treatment Period (cont.)

	Screening	Blinded Treatment Period															
Visit	1	2 BL	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	–4 to–1	w1	w2	w12	w24	w26	w36	w48	w50	w60	w72	w74	w84	w96	w98	w108	w120 [a]
Study Day (window in days)	–28 to–1	1	15 (±2)	85 (±4)	169 (±2)	183 (±2)	253 (±4)	337 (±2)	351 (±2)	421 (±4)	505 (±2)	519 (±2)	589 (±4)	673 (±2)	687 (±2)	757 (±4)	841 (±2)
																	
Pretreatment with IV methylprednisolone [v]		x	x		x	x		x	x		x	x		x	x		x
Administration of IV ocrelizumab or placebo [w]		x	x		x	x		x	x		x	x		x	x		x

β-hCG = β human chorionic gonadotropin; BL = baseline; CD = cluster of differentiation; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; FACS = fluorescence-activated cell sorting; Fc = fragment crystallizable; HAHA = human anti-human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C virus antibody; JCV = John Cunningham virus; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MSFCS = Multiple Sclerosis Functional Composite; PCR = polymerase chain reaction; PK = pharmacokinetic; RCR = Roche Clinical Repository; RPR = rapid plasma reagin; SAE = serious adverse event; SF-36 = Short Form-36; w = week.

[a] Participants who enroll early will require additional 24-week treatment cycles in the blinded treatment period beginning at Week 120. Participants should complete the assessments outlined above. See Table 2 for the schedule of activities for subsequent additional treatment cycles.

[b] **Informed Consent** will be obtained in written form from all participants at screening in order to meet eligibility for the study. Participants who exhibit confirmed disability progression with 24-week confirmation will require written re-consent to continue in the blinded treatment period of the study.

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

Table 1 Schedule of Activities: Screening through the End of Treatment Period (cont.)

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

[e] A structured **telephone interview** will be done on a 4-week basis between visits *up to* 48 weeks after the last infusion to identify and collect information on any changes in the participant's health status (including, new or worsening neurological symptoms) that warrant an unscheduled visit.

[f] **MRI scans**: brain MRI scans should occur within a window of ±4 weeks of the scheduled visit. Brain MRI scans will also be obtained in participants withdrawn from the treatment period (at a withdrawal visit) if not performed during the previous 4 weeks.

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

[h] **Antibody titers**: Measurement of antibody titers against common antigens (mumps, rubella, varicella, and *S. pneumoniae*) will be performed.

[i] **RCR** (DNA) 6 mL whole blood sample to be taken from consenting participants for genetic analysis. If not done at Baseline (Visit 2), sample can be collected at next visit (Visit 3)

[j] **RCR** (RNA) 2 × 2.5 mL whole blood samples to be taken from consenting participants for expression profiling analysis. On infusion visits, samples should be taken prior to methylprednisolone infusion.

[k] **RCR** (Protein) 6 mL blood samples in EDTA tube for plasma will be taken from consenting participants for analysis of protein biomarkers. On infusion visits, samples should be taken prior to methylprednisolone infusion.

[l] **HAHA**: On infusion visits, samples are collected prior to the methylprednisolone infusion.

[m] **PK samples:** On the infusion days (Day 1 and 15) of the first treatment cycle and on infusion day 505 (fourth treatment cycle), 2 blood samples should be collected, one prior to the methylprednisolone infusion, and the second 30 minutes (±10 minutes) following the completion of the ocrelizumab/placebo infusion. For all other infusion visits, a blood sample should be taken before the methylprednisolone infusion. At other times (non-infusion visits), samples may be taken at any time during the visit.

[n] **Clinical genotyping**: a 3 mL whole blood sample will be taken from all participants for analysis of HLA-DR and Fc γ polymorphisms. If not done at Baseline (Visit 2), sample can be collected at next visit (Visit 3).

[o] **Protein biomarker sampling**: a 6 mL blood sample in a plain tube without EDTA for serum sample will be taken from all participants for analysis of protein biomarkers; the sample should be taken prior to methylprednisolone infusion.

[p] **FSH**: FSH only applicable to women to confirm the post-menopausal status.

[q] **Hepatitis** screening and monitoring: all participants must have negative HBsAg result and negative HepCAb screening tests prior to enrollment. If total HBcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 12 weeks.

Table 1 Schedule of Activities: Screening through the End of Treatment Period (cont.)

[r] **FACS**: including CD19 and other circulating B cell subsets, T cells, natural killer cells and other leukocytes. On the infusion days, FACS samples should be collected prior to infusion. See Section 5.13.2 for specific tests.

[s] **Routine safety laboratory tests**. Hematology, chemistry, and urinalysis: On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit.

[t] **Lumbar puncture** will be performed at screening to determine eligibility for the study only in participants who do not have documented CSF results, including original laboratory report and method, demonstrating presence of either an elevated IgG index or one or more oligoclonal bands by isoelectric focusing.

[u] Plasma and urine samples for JCV will be collected at specified timepoints.

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

[w] **Study drug administration**: The Treating Investigator must review the clinical and laboratory re-treatment criteria prior to re-dosing participants with study drug in treatment Cycle 2 and all subsequent treatment cycles.

Table 2 Schedule of Activities: Additional Treatment Cycles, Delayed Dosing, Unscheduled Visits, and Withdrawal from Treatment

	Additional Treatment Cycles [a]			Delayed Dosing Visit [c]	Unscheduled Visit [d]	Withdrawal from Treatment Visit
	Day 1 Additional Treatment Cycle [b] (±2 Days)	Day 15 Additional Treatment Cycle (±2 Days)	12 Weeks Post-Day 1 Infusion Visit (±4 Days)			
						
Physical examination	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x
12 lead ECG						x
Weight						x
Neurological exam	x	x	x		x	x
EDSS, and MSFCS	x		x		x	x
Adverse events	x	x	x	x	x	x
Potential relapses recorded	x	x	x	x	x	x
MFIS, SF-36, EQ-5D						x
Telephone interview (every 4w) [f]	x	x	x			x
Concomitant treatment	x	x	x	x	x	x
MRI [g]						x
Pregnancy test [h]	x	x	x	x	x	x
Antibody titers [i]						x
RCR (RNA) [j]	x					

Table 2 Schedule of Activities: Additional Treatment Cycles, Delayed Dosing, Unscheduled Visits, and Withdrawal from Treatment (cont.)

	Additional Treatment Cycles [a]			Delayed Dosing Visit [c]	Unscheduled Visit [d]	Withdrawal from Treatment Visit
	Day 1 Additional Treatment Cycle [b] (±2 Days)	Day 15 Additional Treatment Cycle (±2 Days)	12 Weeks Post-Day 1 Infusion Visit (±4 Days)			
						
RCR (Protein) [k]	x					
HAHA [l]	x					x
PK samples	x					x
HBV DNA [m]	x		x			x
CD4 count			x			x
IgG			x			
Total Ig, IgA, IgG, IgM	x					x
FACS [n]	x					x
Routine safety laboratory tests [o]	x		x		x	x
Plasma/ urine banking for JCV [p]	x		x			x
Pretreatment with IV methylprednisolone [q]	x	x		x		
Administration of IV ocrelizumab or placebo [r]	x	x		x		

Table 2 Schedule of Activities: Additional Treatment Cycles, Delayed Dosing, Unscheduled Visits, and Withdrawal from Treatment (cont.)

β-hCG = β human chorionic gonadotropin; CD = cluster of differentiation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FACS = fluorescence-activated cell sorting; HAHA = human anti-human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C virus antibody; JCV = John Cunningham virus; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFCS = Multiple Sclerosis Functional Composite; OLE = open-label extension; PCR = polymerase chain reaction; PK = pharmacokinetic; RCR = Roche Clinical Repository; SF-36 = Short Form-36; w = week.

[a] **Additional treatment cycles**: Participants will continue with blinded 24-week treatment cycles until the last participant receives his/her final course of treatment scheduled at Week 98. At that point, all participants will continue to the end of their current (24-week) cycle. If the projected total number of confirmed disability progression events has not been reached at Week 120, then all participants will continue with additional blinded 24-week treatment cycles until the projected number of confirmed disability events has been reached.

[b] Participants undergoing the first infusion of the first additional treatment cycle at Week 120 should also complete all assessments for the Week 120 visit outlined in Table 1.

[c] A **delayed dosing visit** will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests/assessments may be done as appropriate.

[d] **Unscheduled Visit** (non-dosing): Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant. All participants with new neurological symptoms suggestive of MS worsening or of a relapse should have EDSS performed by Examining Investigator. Other tests/assessments may be done as appropriate. Unscheduled visits may also take place during the safety follow-up period.

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

[f] A structured **telephone interview** will be done on a 4-week basis between visits *up to* 48 weeks after the last infusion to identify and collect information on any changes in the participant's health status (including, new or worsening neurological symptoms that warrant an unscheduled visit. For OLE, telephone interviews will be done on a 4-week basis for the first year and every 8-weeks subsequently.

[g] **MRI scans**: brain MRI scans will be obtained in participants withdrawn from the treatment period (at a withdrawal visit) if not performed during the previous 4 weeks. Once the participant has passed the Week 120 visit, brain MRI scans will be performed annually.

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

[i] **Antibody titers**: Measurement of antibody titers against common antigens (mumps, rubella, varicella, and *S. pneumoniae*) will be performed.

Table 2 Schedule of Activities: Additional Treatment Cycles, Delayed Dosing, Unscheduled Visits, and Withdrawal from Treatment (cont.)

[j] **RCR** (RNA) 2×2.5 mL whole blood samples to be taken from consenting participants for expression profiling analysis. On infusion visits, samples should be taken prior to methylprednisolone infusion.

[k] **RCR** (Protein) 6 mL blood samples in EDTA tube for plasma will be taken from consenting participants for analysis of protein biomarkers. On infusion visits, samples should be taken prior to methylprednisolone infusion.

[l] **HAHA and PK samples**: On infusion visits, samples are collected prior to the methylprednisolone infusion

[m] **Hepatitis** screening and monitoring: all participants must have negative HBsAg result and negative HepCAb screening tests prior to enrollment. If total HBcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 12 weeks.

[n] **FACS**: including CD19 and other circulating B cell subsets, T cells, natural killer cells and other leukocytes. On the infusion days, FACS samples should be collected prior to infusion. See Section 5.13.2 for specific tests.

[o] **Routine safety laboratory tests**. Hematology, chemistry, and urinalysis: On infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit. Samples collected during unscheduled visits should preferably be sent to and analyzed by the central laboratory unless results are required urgently.

[p] **Plasma and urine samples for JCV will be collected** at specified timepoints.

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

[r] **Study drug administration**: The Treating Investigator must review the clinical and laboratory re-treatment criteria prior to re-dosing participants with study drug in all subsequent treatment cycles.

Table 3 Schedule of Activities: Safety Follow-Up

	Safety Follow-Up Period					End of Safety Follow-Up or Withdrawal from Study [b]
	Up to 48 Weeks After the Last Infusion: Visits Occur Every 12 weeks (± 7 Days) [a]					
Assessment	12 Weeks Post-Final Treatment Visit [c]	24 Weeks Post-Final Treatment Visit [d]	36 Weeks Post-Final Treatment Visit [e]	48 Weeks Post-Final Treatment Visit [f]	Unscheduled Safety Follow-Up Visit [g]	End of Observation
Routine safety laboratory tests [h]	x	x	x	x	x	x
FACS [i]	x	x	x	x		x
Urine pregnancy test [j]	x	x	x	x	x	x
HBV DNA [k]	x	x	x	x		x
Total Ig, IgA, IgG, IgM		x		x		x
HAHA [l]	x					
PK samples [l]	x					
Neurological examination	x	x	x	x	x	x
EDSS	x	x	x	x	x	x
Physical examination		x		x	x	x
Vital signs		x		x	x	x
Potential relapses recorded	x	x	x	x	x	x
ECG		x		x		x
Adverse events	x	x	x	x	x	x
Concomitant treatment	x	x	x	x	x	x
Telephone interview [m]	x	x	x	x		x
RCR (Protein) [n]		x		x		x

Table 3 Schedule of Activities: Safety Follow-Up (cont.)

	Safety Follow-Up Period					End of Safety Follow-Up or Withdrawal from Study [b]
	Up to 48 Weeks After the Last Infusion: Visits Occur Every 12 weeks (± 7 Days) [a]					
Assessment	12 Weeks Post-Final Treatment Visit [c]	24 Weeks Post-Final Treatment Visit [d]	36 Weeks Post-Final Treatment Visit [e]	48 Weeks Post-Final Treatment Visit [f]	Unscheduled Safety Follow-Up Visit [g]	End of Observation
MRI [o]	----------→				(x)	

β-hCG = β human chorionic gonadotropin; CD = cluster of differentiation; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; FACS = fluorescence-activated cell sorting; HAHA = human anti-human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCR = polymerase chain reaction; PK = pharmacokinetic; RCR = Roche Clinical Repository.

[a] **Safety follow-up:** Safety follow-up will be carried out for 48 weeks starting from the date of last infusion of ocrelizumab. Visits will occur every 12 weeks. As this study will be closed on 31 December 2022, participants already in safety follow-up may complete this study period in the rollover Study MN43964. Safety follow-up applies to study participants who have completed the blinded treatment period (or open-label treatment period, if applicable) and to participants who withdraw early from treatment. *Participants who start treatment with commercial ocrelizumab or another DMT will discontinue from the study completely and will not enter or continue in the safety follow-up period. A Withdrawal from Study visit will be performed at the time of study closure for participants not rolling over to Study MN43964.*

[b] **Withdrawal from Study Visit** for participants withdrawing from the study at any time.

[c] **12-weeks post-final Treatment Visit:** only applies if a participant withdraws from treatment before the mid-cycle visit 12 weeks after the first infusion of the current treatment cycle.

[d] **24-weeks post-final Treatment Visit:** only applies if a participant withdraws from treatment after the mid-cycle visit 12 weeks after the first infusion but before the end of cycle visit (24 weeks after the first infusion) of the current treatment cycle.

[e] **36-weeks post-final Treatment Visit:** applies to study participants who have completed the blinded treatment period (or open-label treatment period, if applicable) and to participants who withdraw early from treatment.

[f] **48-weeks post-final Treatment Visit/*End of Safety follow-up*:** applies to study participants who have completed the blinded treatment period (or open-label treatment period, if applicable) and to participants who withdraw early from treatment.

Table 3 Schedule of Activities: Safety Follow-Up (cont.)

[g] A dedicated (scheduled or unscheduled) safety follow-up visit directly prior to the start of an alternative MS treatment is required for participants who begin an alternative treatment for MS while in safety follow-up in order to assess the participant's clinical status and safety parameters (assessments to be performed as per schedule of activities (Table 3) depending on the study period in which the participant was in when the alternative treatment began).

[h] **Routine safety laboratory tests**: Hematology, chemistry, and urinalysis. Samples collected during unscheduled visits should preferably be sent to and analyzed by the central laboratory unless results are required urgently.

[i] **FACS including** CD19 and other circulating B cell subsets, T cells, natural killer cells and other leukocytes.

[j] **Urine β-hCG [sensitivity** of at least 25 mIU/mL] must be performed in women of childbearing potential during safety follow-up while B cells remain depleted below normal levels. If positive confirm with a serum pregnancy test.

[k] **Hepatitis monitoring**: If total HBcAb is positive at screening, HBV DNA measured by PCR must be negative to be eligible. For those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 12 weeks.

[l] **HAHA and PK samples:** In any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose.

[m] A **structured telephone interview** will be done on a 4-week basis between visits *up to* 48 weeks after the last infusion to identify and collect information on any changes in the participant's health status that warrant an unscheduled visit (including new or worsening neurological symptoms that warrant an unscheduled visit).

[n] **RCR** (Protein) 6 mL blood samples in EDTA tube for plasma will be taken from consenting participants for analysis of protein biomarkers.

[o] MRI should only be performed for participants who begin an alternative treatment for MS, within the time window of 1 month prior to the start of an alternative MS treatment (unless MRI has already been performed within prior 8 weeks).

Table 4 Schedule of Activities: Open-Label Extension Phase

	OLE Phase [a, b]											Delayed Dosing Visit [d]	Unscheduled Visit [e]	Withdrawal from Treatment Visit
Cycle	**1**			**2**		**3**		**4**		**N [c]**				
Visit	**D1**	**D15**	**w12**	**D1**	**w12**	**D1**	**w12**	**D1**	**w12**					
Week in OLE Phase (window in days)	**0 (±5)**	**2 (±5)**	**12 (±7)**	**24 (±5)**	**36 (±7)**	**48 (±5)**	**60 (±7)**	**72 (±5)**	**84 (±7)**	**n (±5)**	**n+12w (±7)**			
Informed consent [f]	x													
Review of eligibility criteria	x													
Review of re-treatment criteria	x	x		x		x		x		x		x		
Physical examination	x	x		x		x		x		x		x	x	x
Vital signs [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12 lead ECG [h]	x					x				(x)				x
Weight (annually)						x				(x)				x
Neurological examination	x	x	x	x	x	x	x	x	x	x	x		x	x
EDSS, and MSFCS	x		x	x	x	x	x	x	x	x	x		x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Potential relapses recorded	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MFIS, SF-36 (once annually)	x				x		x		x		(x)			x
Telephone interview [i]	x	x	x	x	x	x	x	x	x	x	x			x
Concomitant treatment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MRI [j] (once per year)	x					x				(x)				x
Pregnancy test [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Antibody titers [l]	x		x		x		x		x		x			x

Table 4 Schedule of Activities: Open-Label Extension Phase (cont.)

	OLE Phase [a, b]											Delayed Dosing Visit [d]	Unscheduled Visit [e]	Withdrawal from Treatment Visit
Cycle	1			2		3		4		N [c]				
Visit	D1	D15	w12	D1	w12	D1	w12	D1	w12					
Week in OLE Phase (window in days)	0 (±5)	2 (±5)	12 (±7)	24 (±5)	36 (±7)	48 (±5)	60 (±7)	72 (±5)	84 (±7)	n (±5)	n+12w (±7)			
	💉	💉		💉		💉		💉		💉				
HAHA [m]	x													
PK samples [m]	x													
HBV DNA [n]	x		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			(x)
CD4 count			x		x		x		x		x			x
Total Ig, IgA, IgG, IgM	x		x		x		x		x		x			x
FACS [o]	x			x		x		x		x				x
Routine safety laboratory tests [p]	x		x		x		x		x		x			x
RCR (Protein) [q]	x			x		x		x		x				x
Open-label clinical genotyping [r]	x		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			(x)
Pretreatment with IV methylprednisolone and antihistamine [s]	x	x		x		x		x		x		x		
Administration of IV ocrelizumab [t]	x	x		x		x		x		x		x		
Optional samples for RBR (CSF and blood) [u]	x													

Table 4 Schedule of Activities: Open-Label Extension Phase (cont.)

β-hCG = β human chorionic gonadotropin; CD = cluster of differentiation; CSF = cerebrospinal fluid; D = Day; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FACS = fluorescence-activated cell sorting; Fc = fragment crystallizable; HAHA = human anti-human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFCS = Multiple Sclerosis Functional Composite Scale; OLE = open-label extension; PCR = polymerase chain reaction; PK = pharmacokinetic; RBR = Research Biosample Repository; RCR = Roche Clinical Repository;SF-36 = Short Form-36; w = week.

[a] **OLE phase cycles**: The OLE phase will start after the primary analysis and communication from the Sponsor. The OLE phase can terminate at any moment or cycle (see Section 4.1.9). In case the study is ended, a Withdrawal from Treatment Visit should occur *for any participants not rolling over to Study MN43964.*

[b] All participants entering the OLE will receive a dual ocrelizumab infusion (300 mg IV infusions administered 14 days apart) for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks.

[c] The assessments requested for N represent the typical schedule of activities during a cycle.

[d] A **delayed dosing visit** will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests/assessments may be done as appropriate.

[e] **Unscheduled Visit (non-dosing):** Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant. All participants with new neurological symptoms suggestive of MS worsening or of a relapse should have EDSS performed by Examining Investigator. Other tests/assessments may be done as appropriate.

[f] **Informed Consent** for OLE must be signed by the participant prior to the first infusion in the OLE phase.

[g] **Vital signs** will be obtained while the participant is in the semi-supine position (after 5 minutes), including pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature. At infusion visits, the vital signs for all participants should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, vital signs should be obtained prior to the study drug or placebo infusion, then every 15 minutes (±5 minutes) for the first hour; then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion. At non-infusion visits, the vital signs may be taken at any time during the visit.

[h] **ECGs (pre- and postdose)**: ECG should be performed within 45 minutes prior to the methylprednisolone infusion in all participants and within 60 minutes after completion of the ocrelizumab infusion. From OLE Week 72 onwards, ECG assessment is not mandatory; it should only be performed if clinically indicated.

[i] **Telephone interview:** A structured **telephone interview** will be conducted by site personnel every 4 weeks *between visits* to identify and collect information on any changes in the participant's health status that warrant an unscheduled visit (including new or worsening neurological symptoms).

[j] **MRI scans:** A brain MRI scan should be performed at the start of OLE phase if not done in the previous 12 weeks. In the OLE phase, brain MRIs should be done once a year. Brain MRI scans should occur within a window of ±4 weeks of the scheduled visit. Also, brain MRI scans will be obtained in participants withdrawn from the OLE phase (at a withdrawal visit) if not performed during the previous 4 weeks.

[k] **Antibody titers:** Measurement of antibody titers against common antigens (mumps, rubella, varicella, and *S. pneumoniae*) will be performed.

[l] **HAHA**: In any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose.

PK samples: In any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose.

[m] **Hepatitis monitoring:** For those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must continue to be repeated every 12 weeks during the OLE phase.

[n] **FACS:** Including CD19 and other circulating B cell subsets, T cells, natural killer cells and other leukocytes. FACS samples should be collected prior to infusion. See Section 5.13.2 for specific tests.

[o] **Routine safety laboratory tests:** Hematology, chemistry, and urinalysis: On the infusion visit (Cycle 1, Day 1), urine and blood samples should be collected prior to the infusion of methylprednisolone. At all other times, samples may be taken at any time during the visit. Samples collected during unscheduled visits should preferably be sent to and analyzed by the central laboratory and not local unless results are required urgently.

[p] **RCR** (Protein) 6 mL blood samples in EDTA tube for plasma will be taken from consenting participants for analysis of protein biomarkers. Samples should be collected 5–30 minutes prior to methylprednisolone infusion.

[q] Open-label clinical genotyping: A 3 mL whole blood sample will be taken one time from participants that did not have a sample collected for DNA analysis of HLA-DR and Fc γ polymorphisms during the blinded treatment period. If not collected at the first OLE phase visit (Visit 1), the sample may be collected at any subsequent visit.

[r] All participants will receive **prophylactic treatment** with 100 mg of methylprednisolone IV and an oral or IV antihistamine, such as diphenhydramine 50 mg or equivalent dose of alternative, prior to infusion with ocrelizumab. *The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion.* In the rare case when the use of methylprednisolone is contraindicated for the participant, use of an equivalent dose of an alternative steroid (e.g., dexamethasone) should be used as premedication prior to the infusion. It is also recommended that participants receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab infusions.

[s] **Study drug administration:** The Treating Investigator must review the clinical and laboratory re-treatment criteria prior to re-dosing participants with study drug in all subsequent treatment cycles. The participant will need to remain under observation at the clinic for at least 1 hour after infusion. It is anticipated that the participant will need to stay at the hospital or clinic for a full day for the infusion visit.

[t] One-time optional CSF, paired plasma samples, and blood samples for the RBR collected at any timepoint in the OLE phase. These samples should be collected after the participant's consent and at the next possible visit during the OLE phase.

PART I: STUDY DESIGN AND CONDUCT

2. BACKGROUND AND RATIONALE

2.1 BACKGROUND

2.1.1 Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory and degenerative demyelinating disease of the human CNS. It is a global disease that affects an estimated 1.3 million people worldwide, including approximately 630,000 in Europe and 520,000 in the Americas (International Federation of Multiple Sclerosis Societies 2009). The condition manifests as neurological deficits related to damage to the spinal cord, brainstem, optic nerves, cerebellum, and cerebrum. Resulting symptoms may include weakness, pain, visual loss, bowel/bladder dysfunction, and cognitive dysfunction. Diagnosis of MS typically occurs through the application of highly structured diagnostic criteria that rely on clinical observation, neurological examination, brain and spinal cord magnetic resonance imaging (MRI) scans, evoked potentials, and cerebrospinal fluid (CSF) studies (McDonald et al. 2001; Polman et al. 2005).

Multiple sclerosis is clinically subcategorized into 3 phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression (Lublin et al. 2014). These include relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).

Primary progressive MS is a relatively rare form of MS, accounting for approximately 10%–15% of all people with MS. Primary progressive MS is characterized by a progressive course from disease onset without superimposed discrete clinical attacks or relapses (Ebers 2004, Miller and Leary 2007). Unlike RRMS, the typical age of onset for PPMS is older at approximately 40 years, and men are affected nearly as often as women (Cottrell et al. 1999). The absence of relapses imposes special challenges for diagnosis, requiring clinical evidence that the disease has advanced for at least 1 year from symptom onset (McDonald et al. 2001; Polman et al. 2005).

Natural history studies of patients with PPMS suggest a disabling course from symptom onset. In a well-characterized cohort of patients with PPMS from Ontario, Canada, the median time to the use of a unilateral cane or brace (Disability Status Scale 6 [DSS 6]) was 8 years and the median time to wheelchair use (DSS 7) was under 20 years (Cottrell et al. 1999). A higher proportion of patients with PPMS present initially with motor impairment, cerebellar ataxia and brainstem symptoms than patients with relapsing-onset, and spastic paraparesis is a common early clinical presentation (Andersson et al. 1999).

No treatment has been demonstrated to significantly slow the progression of disability in patients with PPMS, including therapies approved for the treatment of relapsing forms of

MS. A large Phase III randomized, controlled trial with glatiramer acetate (Wolinsky et al. 2007) and smaller randomized, controlled clinical trials evaluating mitoxantrone (Kita et al. 2004), interferon (IFN)-β-1a intramuscularly (IM; Leary et al. 2003), and IFN-β-1b (Montalban 2004) did not demonstrate a significant impact on clinical progression in the PPMS population. The most recently completed randomized, controlled PPMS clinical trial was the 439-participant Phase II/III Study U2786g (OLYMPUS), comparing rituximab with placebo over a 96-week treatment period. Overall, this study did not demonstrate a significant treatment effect. Subgroup analyses suggested that a younger, more active subset of participants with PPMS (defined by the presence of gadolinium [Gd]-enhancing lesions seen on MRI scans at baseline and higher lifetime rates of disability progression) may have benefitted clinically from anti-CD20 therapy (Hawker et al. 2009). Currently, PPMS remains a severely disabling condition with very high unmet medical need.

2.1.2 Ocrelizumab

Ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) is a humanized, glycosylated monoclonal antibody directed against the CD20 antigen present on select normal, as well as malignant B cells. Cluster of differentiation (CD)20 is a B cell surface molecule that is restricted in expression to pre–B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Ocrelizumab shares a similar basic mechanism of action as rituximab (MabThera®/Rituxan®), a chimeric monoclonal antibody also directed against the CD20 antigen. Clinical experience with rituximab has demonstrated B cell depletion to be of major clinical benefit for the treatment of certain lymphoma types and rheumatoid arthritis (RA). The safety and efficacy of ocrelizumab was evaluated in multiple randomized, controlled Phase III clinical trials in MS and RA (see below) and a Phase II study in RRMS (see Section 2.1.4).

2.1.2.1 History of Ocrelizumab

The first human experience with ocrelizumab in autoimmune conditions was from 2 Phase I/II dose-escalating studies (ACT2847g [Genovese et al. 2008] and WA18230) in participants with active RA. In these studies, ocrelizumab was found to be generally well-tolerated in participants with RA, and no unanticipated safety concerns were observed when compared with data from participants with RA treated with rituximab. More detailed information from completed studies regarding the nonclinical and clinical results with ocrelizumab is provided in the Ocrelizumab Investigator's Brochure.

The development programs for RA and lupus have been terminated. The analyses of efficacy and safety data from the Phase III studies in RA led the Sponsors to conclude that ocrelizumab 200 mg × 2 provided no additional benefit to currently available therapies in the target population of patients with TNF-IR, while ocrelizumab 500 mg × 2 demonstrated an unfavorable safety profile (higher serious infection rate). The unfavorable safety profile of ocrelizumab 500 mg × 2 was driven mainly (although not

entirely) by participants recruited from Asia. The Sponsor concluded that these observations do not support further development of this therapy in RA.

As a result of the limited number of participants (33 participants) enrolled in Study WA20499 (systemic lupus erythematosus study) at the time of the study termination; no meaningful analysis of efficacy could be conducted. Study WA20500 (LN study) was terminated prior to the timing of the primary endpoint.

2.1.3 Rationale for Targeting B Cells in Multiple Sclerosis

Humoral immunity has been implicated in MS for decades, as evidenced by inclusion of CSF oligoclonal bands and increased intrathecal IgG synthesis in diagnostic criteria for MS (McDonald et al. 2001; Polman et al. 2005; Sidén 1979). Although, until very recently, the prevailing view of MS pathophysiology held that the CNS inflammation seen in MS is principally mediated by CD4+ pro-inflammatory (Th1, Th17) T cells, rapidly expanding evidence suggests that B cells may contribute to MS pathogenesis much more than was previously believed, potentially through either antibody-dependent or independent mechanisms (Meinl et al. 2006; Franciotta et al. 2008; McFarland 2008).

B lymphocytes have been detected within MS lesions and in the CSF of patients with MS. Molecular analysis of both lesional and CSF B cell repertoires revealed dominant, clonally-expanded B cell populations exhibiting somatic hypermutation in the antigen-recognizing CDR3 regions of Ig heavy chains, predominately within the *VH4* gene family (Owens et al. 1998; Qin et al. 1998; Baranzini et al. 1999; Colombo et al. 2000; Ritchie et al. 2004; Lambracht-Washington et al. 2007; Owens et al. 2007). Detection of these affinity-matured, clonally-expanded repertoires in the CSF but not in the peripheral blood of patients with MS suggests that a localized, antigen-driven B cell response is present in the CNS compartment. Cerebrospinal fluid clonal B cell expansion has been reported in participants with both RRMS and PPMS shortly after diagnosis, implying a role for B cells early in MS pathogenesis rather than as a late response to longstanding tissue damage (Monson et al. 2005). More recently, cDNA transcriptomes of clonally-expanded affinity-matured B cells isolated from the CSF of participants with MS have been sequence-matched to specific IgG oligoclonal bands from the same CSF samples, indicating that this longstanding hallmark of MS diagnosis derives from identifiable B cell clones present in the CNS compartment (Obermeier et al. 2008).

Many hypotheses for the role of B cells in MS have been postulated. B cells may differentiate into plasma cells and produce CNS-directed autoantibodies, potentially triggering cellular and complement-dependent cytotoxicity. Although a pathogenic role of antimyelin antibodies in MS has not been established, they have been detected in the CSF of patients with MS (Reindl et al. 1999; Egg et al. 2001; Andersson et al. 2002) and in active MS lesions (Genain et al. 1999), and remain potential candidates as effectors of myelin sheath damage. B cells may also function as antigen presenting cells and

thereby modulate effector T cell responses, as they exhibit regulated secretion of both pro-inflammatory and anti-inflammatory cytokines, a function that appears to be abnormal in patients with MS (Meinl et al. 2006). Finally, B cells may be a site of latent viral infections such as Epstein-Barr virus, which may drive CNS autoimmune responses through molecular mimicry or other pro-inflammatory mechanisms (Franciotta et al. 2008).

Post-mortem pathological studies have identified the presence of ectopic follicular lymphoid structures in the meninges anatomically proximal to sites of grey-matter demyelination in a subset of patients with SPMS (Serafini et al. 2004; Kutzelnigg et al. 2007; Magliozzi et al. 2007). Similar tertiary lymphoid structures form de novo in various tissues of many autoimmune disorders and represent potential de novo sites of chronic autoantigenic B cell activation, maturation and clonal expansion (Aloisi and Pujol-Borrell 2006). Patients with SPMS exhibiting these lymphoid structures have been found to have worse progression rates, when compared with controls without such follicular structures (Howell et al. 2009) and a pathomechanistic link to grey-matter demyelination typical for SPMS has been suggested. Although tertiary lymphoid structures have not been described in the small number of patients with PPMS studied, grey-matter demyelination is prominent in brain specimens from both patients with SPMS and PPMS, and it is conceivable that the same pathomechanism as suggested in SPMS may apply for PPMS. Whether or not an anti-CD20 therapeutic antibody can affect the formation or persistence of meningeal lymphoid follicles or the grey-matter demyelination prominent in progressive forms of MS is unknown.

In summary, B lymphocytes are believed to contribute to the pathogenesis of all subtypes of MS, including PPMS. Removing select peripheral B cells from circulation may beneficially disrupt inflammatory processes that potentially involve chronic antigenic stimulation or other regulatory functions promoting chronic autoimmunity. Ocrelizumab specifically depletes CD20+ B cells, making it a potentially attractive pharmacological agent to test therapeutic potential in patients with PPMS.

2.1.4 Sponsor Experience with Anti-CD20 Compounds in Multiple Sclerosis

2.1.4.1 Ocrelizumab in RRMS

Study WA21493/ACT4422G was a 220-participant Phase II, multicenter, randomized, parallel-group, placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of 2 dosing regimens of ocrelizumab (1000 mg×2 [administered on Day 1 and Day 15, followed by single infusions of 1000 mg for subsequent cycles] and 300 mg×2 [administered on Day 1 and Day 15, followed by single infusions of 600 mg for subsequent cycles]), with an additional randomized open-label arm of IFN β–1-a 30 μg IM every week. The primary objective was to evaluate the efficacy of 2 dosing regimens of ocrelizumab compared with placebo in reducing brain inflammation, as measured by the total number of Gd-enhancing T1 lesions observed on serial MRI scans

of the brain at Weeks 12, 16, 20, and 24. Key secondary objectives were to evaluate the efficacy of both dosing regimens of ocrelizumab compared with placebo in reducing annualized relapse rate (ARR) at Week 24 and to evaluate the safety and tolerability of both dosing regimens of ocrelizumab in participants with RRMS. Exploratory outcomes included analysis of both dosing regimens of ocrelizumab compared with IFN β-1-a 30 μg IM weekly for various study measures. Treatment with ocrelizumab was planned for 72–96 weeks total, depending on the study arm (participants from both the placebo and the IFN β-1a group switched to ocrelizumab 300 mg × 2 after Week 24). Additional MRI scans of the brain will be obtained at Weeks 96 and 144 for a subgroup of participants.

Week 24 results demonstrated that both doses of ocrelizumab achieved the primary endpoint by significantly reducing the number of Gd-enhancing lesions compared with placebo ($p < 0.0001$). Both ocrelizumab dose groups showed statistically significant reductions in ARR compared with the placebo group (ARR = 0.125 for the ocrelizumab 300 mg × 2 group [$p = 0.0005$] and ARR = 0.169 for the ocrelizumab 1000 mg × 2 group [$p = 0.0014$] compared with ARR = 0.637 for the placebo group), representing a relative reduction (RR) of 80% and of 73% in ARR vs. the placebo group for the low dose and the high-dose ocrelizumab groups, respectively. In exploratory analyses, both ocrelizumab groups were superior to the IFN β-1a group for the primary endpoint ($p < 0.0001$) and the 300 mg × 2 group for ARR (ARR = 0.364 for the IFN β-1a group, representing an RR of 66% in ARR with $p = 0.03$ for the ocrelizumab 300 mg × 2 group vs. the IFN β-1a group and a RR of 53.6% in the ARR with $p = 0.086$ for the ocrelizumab 1000 mg × 2 group vs. the IFN β-1a group; Kappos et al. 2011).

Participants from both the placebo and IFN β-1a groups switched to ocrelizumab 300 mg × 2 after Week 24. By 48 weeks, the level of benefit of ocrelizumab in reduction of ARR was maintained; participants in the ocrelizumab 300 mg × 2 group continued to have a suppressed ARR of 0.086 from Weeks 24–48, and participants who switched to ocrelizumab from either placebo or IFN β-1a derived a similar degree of efficacy to those randomized to ocrelizumab from onset (ARR for placebo-to-ocrelizumab = 0.161 and for IFN β-1a-to-ocrelizumab = 0.137 after the switch, representing a RR of 74% and 62.4% compared with ARR before the switch, respectively). From Weeks 0–72, participants originally randomized to ocrelizumab 300 mg × 2 maintained clinical efficacy with an ARR of 0.186.

The most commonly reported adverse events in ocrelizumab-treated participants were infusion-related reactions (IRRs). Infusion-related reactions were reported during/after the first infusion (Day 1) for 30%–43.6% of participants treated with ocrelizumab. Fewer participants (2.1%–9.4%) experienced IRRs during/after the second infusion (Day 15). The most common symptoms were rash, pruritus, flushing, tachycardia, headache, pyrexia, and throat irritation. No unanticipated, clinically significant

abnormalities in vital signs, ECGs, or laboratory parameters were observed in association with ocrelizumab treatment.

On review of the placebo-controlled, double-blinded, 24-week safety data, no imbalance in adverse events (or infection adverse events) or serious adverse events (or infection serious adverse events) between the placebo and the active ocrelizumab arms was observed. The rate of adverse events (or infection adverse events) and serious adverse events (or infection serious adverse events) did not increase in ocrelizumab-treated participants at Week 48 compared with Week 24. No trend toward an increased risk of adverse events (or infection adverse events) or serious adverse events (or infection serious adverse events) was found for ocrelizumab-treated participants with previous IFN treatment (for 6 months).

By the time all participants finished Week 48 of treatment, the incidence of infections and serious infections was 92.41/100 participant-years (PY) (95% CI: 76.59, 111.5) and 3.39/100 PY (95% CI: 1.27, 9.04) in participants exposed to low-dose ocrelizumab, including participants who switched from placebo or IFN β-1a. The incidence of infections and serious infections was 97.38/100 PY (95% CI: 74.76, 126.84) and 5.31/100 PY (95% CI: 1.71, 16.47) in those exposed to the high dose of ocrelizumab. The most common infections in ocrelizumab-treated participants included urinary tract infections, upper respiratory infections, and nasopharyngitis.

To date, in Study WA21493, after over 250 participant-years of exposure to ocrelizumab, no reports of opportunistic or fatal infections have been made.

Please refer to the Ocrelizumab Investigator's Brochure for more information.

2.1.4.2 Rituximab in RRMS

Two clinical trials of rituximab have been conducted in participants with RRMS. Rituximab is a chimeric mouse/human monoclonal antibody that shares the same basic mechanism of action as ocrelizumab. Findings briefly highlighted below offer additional support for the therapeutic potential of the anti-CD20 mechanism in MS.

Study U3264g (HERMES Jr.) was a Phase I, open-label, multicenter study in 26 adults with RRMS to evaluate the safety and tolerability of 2 treatment cycles of rituximab administered at baseline and after 24 weeks. Re-treatment with rituximab (1000 mg × 2) at 24 weeks was safe and well-tolerated and resulted in an observed decrease in relapses and Gd-enhancing lesions through 72 weeks (Bar-Or et al. 2008).

Study U2787g (HERMES) was a Phase II, proof-of-concept, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of rituximab in 104 adults with RRMS. The primary objectives were to investigate the efficacy of rituximab compared with placebo, as measured by the total number of

Gd-enhancing T1 lesions observed on serial MRI scans of the brain at Weeks 12, 16, 20, and 24, and to evaluate the safety and tolerability of rituximab in participants with RRMS. Secondary objectives were to evaluate additional MRI parameters and the proportion of participants relapsing. The trial met its primary efficacy endpoint and all secondary endpoints. Rituximab was safe and generally well-tolerated in this study through 48 weeks, although the rate of infusion-associated adverse events, particularly after the first infusion, was higher in rituximab-treated participants (78%) than in participants who received placebo (40%). Corticosteroid premedication was not administered before or at the time of infusion. Study U2787g provides proof of the principle that an anti-CD20 therapeutic approach can reduce both MRI and clinical evidence of inflammatory activity in adults with RRMS (Hauser et al. 2008).

2.1.4.3 Rituximab in PPMS

A single, Phase II/III, randomized, double-blinded, placebo-controlled trial of rituximab for PPMS was conducted. The findings summarized below represent the largest and longest duration trial experience to date evaluating the safety and efficacy of anti-CD20 therapy in individuals with MS.

Study U2786g (OLYMPUS) was a Phase II/III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study evaluating the safety and efficacy of rituximab in participants with PPMS over a 96-week treatment period consisting of 4 treatment cycles with dual infusions of 1000 mg (2000 mg/cycle). Although the trial did not demonstrate significant primary efficacy on time to confirmed disease progression as measured by the Expanded Disability Status Scale (EDSS), a difference was observed: 38.5% of participants in the placebo group experienced confirmed disease progression vs. 30.2% in the rituximab group. Biological activity was evidenced by significantly lower T2 lesion volume accumulation on brain MRI, a secondary efficacy endpoint, in rituximab-treated participants compared with those who received placebo ($p = 0.0008$).
Subgroup analyses suggest that participants with PPMS and evidence of active disease may have shown significant clinical treatment response as measured by time to confirmed disease progression over a 96-week timeframe. Factors that appeared prognostic for disease progression and potentially predictive of treatment response in the rituximab group included younger age, presence of contrast-enhancing lesions at baseline on brain MRI, and higher MS severity score.

Rituximab was generally safe and well-tolerated in Study U2786g. The proportions of participants with at least 1 adverse event (100% for placebo vs. 99% for rituximab) and 1 serious adverse event (13.6% for placebo vs. 16.1% for rituximab) were comparable between treatment groups. Three adverse events that occurred during the study led to death: 1 adverse event in the rituximab group following recurrent aspiration pneumonias and 2 adverse events in the placebo group because of pneumonia and cardiopulmonary failure. More infusion-associated adverse events were observed in rituximab-treated participants (73.6% for rituximab vs. 40.3% for placebo), particularly after the first

infusion, but rates declined in both groups to similar levels upon successive infusions. Participants were not pre-medicated with glucocorticoids before rituximab infusions in Study U2786g. The vast majority (92%) of infusion-associated events in rituximab-treated participants were mild to moderate in severity; no Grade 4 or 5 infusion-associated events were observed. The proportion of participants with at least 1 infection was comparable between groups (68.2% for rituximab vs. 65.3% for placebo), but a higher proportion of participants with at least 1 serious infection was observed in the rituximab-treated group (4.5%) compared with placebo (<1%). No opportunistic infections occurred.

Treatment with rituximab was associated with rapid and near-complete depletion of circulating CD19+ B lymphocytes beginning 2 weeks post-treatment through 96 weeks. Approximately 35% of rituximab-treated participants had recovered peripheral CD19 B cell counts to 80 cells/μL (the laboratory defined lower limit of normal [LLN] in healthy volunteers) within 48 weeks after the last dose. Median circulating CD3 T-lymphocyte counts were not appreciably altered by rituximab. At any time in the trial, IgM levels were below the LLN in 31.7% of rituximab-treated participants and 5.9% of placebo-treated participants. The proportions of participants with IgG and IgA levels below LLN were not different between groups. The incidence of infectious adverse events and infectious serious adverse events did not appear higher in participants with Ig levels (all isotypes) below LLN in either treatment group compared with participants with Ig levels in the normal range or above upper limit of normal (ULN; Hawker et al. 2009).

2.2 RATIONALE FOR THE STUDY *AND BENEFIT–RISK ASSESSMENT*

This study (WA25046) is a pivotal Phase III clinical trial composed of a blinded treatment period, an open-label extension (OLE) phase, and a safety follow-up period. The blinded treatment period is designed to demonstrate the efficacy and safety of ocrelizumab in PPMS in comparison with placebo. The OLE serves to evaluate long-term safety, tolerability, and efficacy of ocrelizumab treatment in participants with PPMS.

This study is part of a broader, confirmatory clinical development program investigating the safety and efficacy of ocrelizumab in participants with both relapsing MS (RMS) and PPMS. An OLE phase of the Phase II Study WA21493/ACT4422G is ongoing for eligible participants with RRMS. There are 3 ongoing Phase III pivotal trials (including the one presented in this protocol), 2 trials in RMS and 1 trial in PPMS. Please see Section 4.1.5 for further details on study design and to the Ocrelizumab Investigator's Brochure, for more information on efficacy and safety.

A benefit–risk assessment was conducted to determine whether there is any impact on the concomitant use of SARS-CoV-2 vaccines on the conduct of this study. Based on

this assessment, no impact is anticipated to affect the efficacy and safety in participants enrolled in ocrelizumab clinical trials. Existing information on identified risks, safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) provided in the study protocol (namely, immunization [Section 5.5.3], concomitant therapy [Section 5.5], and impaired response to vaccination [Section 7.3.1.1]) are considered adequate.

Data from the pivotal Phase III studies of ocrelizumab in RMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. The vaccination study (BN29739, VELOCE) showed that participants with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The antibody immune response was considered protective, albeit with reduced levels of antibodies compared with controls. In this study, vaccines were given as early as 12 weeks after the first ocrelizumab infusion (and as early as 10 weeks after the second ocrelizumab infusion of the first dose). Boosters were given at least 4 weeks before the next dose of ocrelizumab. Other immune responses such as cellular responses were not investigated in the Study BN29739.

Roche is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the SARS-CoV-2 vaccine in ocrelizumab–treated participants.

As with any other medication or vaccine, SARS-CoV-2 vaccines should be reported as concomitant medication by using the standard fields in the clinical database (see Section 5.5).

2.2.1 Statement of Therapeutic Equipoise

The ethics of controlled clinical trials require that therapeutic equipoise exist between comparative treatments. In the case of Study WA25046, therapeutic equipoise does exist for a placebo-controlled trial of ocrelizumab despite a negative primary result of the Study U2786g in PPMS comparing placebo with rituximab (see Section 2.1.4.3), a molecule that shares a similar basic mechanism of action to ocrelizumab. Although the study did not demonstrate significant primary efficacy on time to confirmed disease progression as measured by EDSS, a lower proportion of participants in the rituximab group experienced confirmed disease progression (30.2%) compared with placebo (38.5%). Rituximab did demonstrate biological activity by significantly reducing T2 lesion volume accumulation on brain MRI over 96 weeks compared with placebo. Pre-specified subgroup analyses also suggest that younger participants with PPMS with evidence of active disease (presence of Gd-enhancing lesions and/or duration of disease $\leq$3 years) may have shown significant clinical signs of treatment-related benefit as measured by time to confirmed disability progression over a 96-week timeframe.

Clinical trial design considerations may also have contributed to the negative result of Study U2786g, rendering premature any definitive conclusion that the anti-CD20 therapeutic mechanism is ineffective in PPMS. The duration of the treatment period in Study U2786g was 96 weeks, while most Phase III trials using similar EDSS outcome measures in progressive forms of MS (i.e., PPMS and SPMS) have been designed with a minimum 3-year treatment period. Subgroup analyses also suggest that some participants who were less likely to benefit from an anti-CD20 therapeutic approach were included in the study, as well as many less active participants whose EDSS did not worsen over 96 weeks despite receiving placebo treatment. Finally, the study was designed in the absence of prior trial data on the effect of anti-CD20 antibodies in individuals with PPMS. Thus, a statistical powering assumption targeting a 50% RR in confirmed disease progression over 96 weeks appears to have been overly optimistic.

The primary hypothesis that an anti-CD20 monoclonal antibody, such as ocrelizumab, may confer clinical benefits as compared with placebo in a PPMS population has neither been adequately proven nor disproven. Based on these considerations, a randomized, controlled Phase III treatment trial comparing ocrelizumab with placebo is ethically justified within the framework of therapeutic equipoise.

2.2.2 Statement on the Use of Placebo Comparator

Primary progressive MS is a neurologically disabling condition without a DMT. To date, no therapies have shown effectiveness in PPMS and none are registered for its treatment in any global region. Pursuant to the Helsinki Declaration, when standard treatment of a disease exists, placebo should generally not be used in clinical trials (World Medical Association 2008). However, Paragraph 32 of the Declaration supports the stance that placebo can be acceptable in the setting where no proven standard therapy exists:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the participants who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

Given that no standard therapy exists for the treatment of PPMS, a placebo-controlled trial is acceptable provided that appropriate participant consent and safeguards are instituted to minimize the risk of serious or irreversible harm resulting from exposure to placebo.

The use of placebo in a PPMS clinical trial is also ethically justified according to the global MS scientific community. In recent years, ethical considerations regarding placebo-controlled clinical trials in the subtypes of MS have been publicly discussed and debated. A recent publication, "Ethics of placebo-controlled trials in multiple sclerosis" (Polman et al. 2008), reflects a consensus position of international clinical and scientific MS experts following a 2007 meeting sponsored by the U.S.-based National Multiple Sclerosis Society. The reference clearly notes that no established effective therapy currently exists for PPMS and supports the ethicality of appropriately designed placebo-controlled trials in this participant population.

3. OBJECTIVES

3.1 PRIMARY OBJECTIVE

To investigate the efficacy of ocrelizumab compared with placebo in participants with PPMS, as measured by the time to onset of confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks, based on regularly scheduled visits.

Disability progression is defined as an increase of $\geq$1.0-point from the baseline EDSS when the baseline score is 5.5 or less, and $\geq$0.5 when the baseline score is more than 5.5, that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication). See Section 8 for further details.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate the efficacy and safety of ocrelizumab compared with placebo, as reflected by the following:

- The time to onset of confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 24 weeks, based on regularly scheduled visits
- The change in Timed 25-Foot Walk Test (T25FWT) from baseline to Week 120
- The change in total volume of T2 lesions on MRI scans of the brain from baseline to Week 120
- The percentage change in total brain volume as detected by brain MRI from Week 24–120
- The change in SF-36 Health Survey (SF-36) version 2 Physical Component Summary (PCS) score from baseline to Week 120
- To evaluate the safety and tolerability of ocrelizumab 300 mg$\times$2 (over 24-week treatment cycles) compared with placebo in participants with PPMS

3.3 EXPLORATORY OBJECTIVES

The exploratory objectives in this study will include, but may not be limited to, the following evaluations.

Clinical:

- The proportion of participants with confirmed 12-week disability progression at Week 120
- The change in EDSS score (mean change and area under the concentration–time curve [AUC]) from baseline to Weeks 48, 96, and 120
- The change in Multiple Sclerosis Functional Composite Scale (MSFCS) score from baseline to Weeks 48, 96, and 120
- The time to confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks (0.5 or 1, same criteria as for the primary endpoint time to 12-week CDP) or a 20% increase in T25FWT that is sustained for at least 12 weeks, or a 20% increase in the 9-Hole Peg Test (9-HPT) that is sustained for at least 12 weeks
- The time to sustained 20% increase in the T25FWT and 9-HPT
- The proportion of participants with a 20% increase in T25FWT time
- The proportion of participants with a 20% increase in 9-HPT time
- The change in Paced Auditory Serial Addition Test (PASAT) from baseline to Week 120

Imaging:

- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 lesions as detected by brain MRI
- The percentage change in cortical grey matter volume from baseline to Week 120
- The percentage change in white-matter volume from baseline to Week 120
- The change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain

Participant-Reported Outcomes:

- The change in fatigue, as measured by the Modified Fatigue Impact Scale (MFIS) total score and subscale scores (Physical Impact, Cognitive Impact, and Psychological Impact) from baseline to Week 120
- The change in quality of life, as measured by the SF-36 Mental Component Summary (MCS) score from baseline to Week 120

Biomarkers:

- To investigate the pharmacokinetics and other pharmacodynamic study endpoints of ocrelizumab

- To explore the impact of ocrelizumab therapy on biomarkers associated with the proposed inflammatory or neurodegenerative process in PPMS

OLE Phase:

- To evaluate the long-term safety of ocrelizumab treatment during the OLE phase of the study
- To evaluate the long-term effects of ocrelizumab on clinical and MRI parameters of disease activity and progression during the OLE phase of the study

3.4 RESEARCH BIOSAMPLE REPOSITORY OBJECTIVES

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides).

Specimens stored in the RBR will be used to:

- *Study the association of biomarkers with efficacy and/ or adverse events associated with ocrelizumab*
- *Increase the knowledge and the understanding of the biology of MS and mode of action of ocrelizumab*

Similarly, the RBR samples collected in the OLE phase of this study will be used for research into MS disease progression mechanisms, identification of new MS disease progression biomarkers, and the development of new therapeutic agents.
See Section 5.16 for details on the RBR.

3.5 OPTIONAL EXPLORATORY SUBSTUDIES

Consenting participants who enrolled in the main Study WA25046 and who are eligible will be offered the opportunity to participate in optional substudies, which are run under separate protocols. See Section 5.22 for details.

3.5.1 Optical Coherence Tomography Exploratory Substudy

This substudy is run under the main study protocol and will be conducted at certain selected centers and will be used to evaluate the neuroprotective effect of ocrelizumab as measured by retinal nerve fiber layer (RNFL) thickness and macular volume in both eyes (see Section 5.22.1 and Appendix 6).

In July 2017, Roche determined that sufficient data had been collected from the optical coherence tomography (OCT) substudy. During 2017 and 2018, participants will be discontinued from the OCT substudy but may continue in the OLE.

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

This is a Phase III, randomized, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of two 300 mg ocrelizumab IV infusions of separated by 14 days at a scheduled interval of every 24 weeks as compared with placebo in adults with PPMS. Participants will be treated for a minimum of 120 weeks representing at least five 24-week treatment cycles. The study will enroll approximately 630 participants in a 2:1 randomization (ocrelizumab:placebo), globally. Randomization will be performed through an Interactive voice or Web-based response system (IxRS) and will be stratified by region (U.S. vs. Rest of World [ROW]) and age ($\leq$45 vs. $>$45).

This study consists of the following study periods: a screening period, a blinded treatment period, an OLE phase, and a safety follow-up period. The study duration will vary for each participant to maximize the safety and efficacy data collected, as described below.

4.1.1 Screening Period

The screening period lasts up to 4 weeks.

4.1.2 Blinded Treatment Period

All participants will undergo at least 120 weeks of study treatment representing 5 treatment cycles, each of 24 weeks' duration. The study will be unblinded when the last enrolled participant completes at least 120 weeks (5 cycles) of study treatment, provided the total number of confirmed disability progression events is approximately 253 (based on the Sponsor's best estimation after the last participant finishes Week 108 visit), or at the latest when the last randomized participant has been in the blinded treatment period for 3 years.

If the projected number of confirmed disability progression events has not been reached by Week 120 because of slower than anticipated disability progression rates, the treatment period will be extended until approximately 253 confirmed disability progression events have occurred, with additional treatment cycles every 24 weeks, in order to maintain statistical power to detect a treatment difference. Because it is anticipated that it may take 12–18 months to recruit participants, this blinded treatment period may extend to up to 3.5–4 years for the first group of participants enrolled into the study.

If the last participant enrolled discontinues the treatment period before Week 120 or before 3 years of blinded treatment, the date of 120 weeks or 3 years after his/her randomization date will be used.

Randomization (Day 1) will occur only after the participant has met all inclusion and exclusion criteria. For the first treatment cycle and in subsequent treatment cycles of

study drug every 24 weeks, participants will be dosed 14 days apart (300 mg ocrelizumab or placebo infusion × 2). All participants will also receive a 100 mg methylprednisolone IV infusion on Day 1 and with each subsequent ocrelizumab or placebo infusion. In participants where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication. More detailed information on study drug administration is contained in Section 6.

4.1.3 Open-Label Extension Phase

Following database lock of the blinded treatment period, participants should continue to receive blinded treatment, as per the schedule of activities (Table 2), until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor.

Upon the disclosure of results and a positive benefit–risk assessment of the use of ocrelizumab therapy, participants who completed the blinded treatment period and who, in the opinion of the investigator, could benefit from treatment may receive open-label ocrelizumab. Unless the Sponsor decides to terminate the ocrelizumab program for MS, the OLE phase will continue as per local regulation. This decision will be based on the change of benefit–risk and safety monitoring. Eligible participants need to provide consent for participation in the OLE phase. Unless *discontinued* early, all participants may continue their treatment with open-label ocrelizumab as per the protocol until 31 December 2022. All participants must discontinue open-label ocrelizumab treatment *within this study* before 31 December 2022. *However, participants will be offered continuation of ocrelizumab treatment or a safety follow-up period via a rollover study (MN43964, OLERO).*

Participants who start treatment with commercial ocrelizumab *or another DMT* will discontinue from the study completely and will not enter the safety follow-up period.

Participants who are not willing to participate in the OLE phase of the study will enter the safety follow-up period (see below). In the case of a participant who initially declines participation in the OLE phase and subsequently changes their decision, the participant may be deemed eligible to enter the OLE phase up to 24 weeks after the OLE phase begins. This will occur on a case-by-case basis in consultation with the Sponsor.

Participants who consent to participate in the OLE phase will be required to meet the treatment/re-treatment criteria prior to infusion with ocrelizumab. During the OLE phase, all participants will receive dual IV infusions of ocrelizumab 300 mg × 2 for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single 600 mg ocrelizumab IV infusion every 24 weeks (see Table 4 and Section 5.23 for more details). The rationale for the switching to a single infusion for the subsequent cycles is

provided in Section 4.1.6. Participants who withdraw from the OLE phase will be entered into the safety follow-up period (see below).

4.1.4 Safety Follow-Up Period

The safety follow-up period will begin when the participant completes or discontinues from the blinded treatment period or OLE phase for any reason. Participants should remain in the safety follow-up period for *up to* 48 weeks following the last infusion of study drug/open-label ocrelizumab (as applicable).During the safety follow-up period, participants will be assessed at clinical visits every 12 weeks. Telephone interviews will be performed every 4 weeks *between visits*.

Participants who start commercial ocrelizumab *or another DMT* will be discontinued from the study completely and will not enter or continue in the safety follow-up period.

Because this study will be closed on 31 December 2022, participants already in safety follow-up may complete this study period in the rollover Study MN43964.

It is important to distinguish between "withdrawal from treatment" and "withdrawal from study". Participants who withdraw from treatment should be encouraged to remain in the study for the full duration of the safety follow-up period (*up to* 48 weeks from the last infusion).

Every effort should be made to ensure that participants who withdraw from study treatment complete the safety follow-up period and all related assessments, regardless of whether or not they receive alternative treatment for MS.

Table 5 Overview of the Study Design and Dosing Regimen

	Blinded Treatment Period												OLE Phase		
	5 Treatment Cycle (120 Wks) Minimum [a, b, c, d, h]												Variable [a, c, e ,f, g, h]		
	1st Cycle (Wks 0–24)		2nd Cycle (Wks 24–48)		3rd Cycle (Wks 48–72)		4th Cycle (Wks 72–96)		5th Cycle (Wks 96–120)		Additional Treatment Cycles [b, d] (Every 24 Wks)		Open-Label Treatment Cycle 1 [f, h]		Open-Label Treatment Cycles [b ,c...N f, h] (Every 24 Wks)
Randomization group	**Day 1**	**Day 15**	**Wk 24**	**Wk 26**	**Wk 48**	**Wk 50**	**Wk 72**	**Wk 74**	**Wk 96**	**Wk 98**	**Wk 120 (Day 1)**	**Wk 120 (Day 15)**	**Open-label Day 1**	**Open-label Day 15**	**Open-label Day 1**
A Ocrelizumab	Ocrelizumab 300 mg IV														
B Placebo	Placebo IV												Ocrelizumab 300 mg IV		

OLE=open-label extension; Wk=week(s).

[a] Each treatment cycle has a duration of 24 weeks.

[b] The blinded treatment period consists of a 120–week minimum period. Participants enrolled early in the study will undergo up to an estimated 2–3 additional treatment cycles, depending on the duration of enrollment and the total number of disability progression events.

[c] After the first infusion, an evaluation will be performed before each subsequent infusion to ensure that the participant remains eligible for re-treatment (see Section 6.2.3).

[d] Trial participants entering the study early will undergo more than 5 treatment cycles. When applicable, subsequent dosing cycles will consist of the same dosing regimen at 24-week intervals as Cycles 2–5.

[e] The OLE phase for eligible participants begins after the primary database lock at the completion of the blinded treatment period. The OLE phase can terminate at any moment or cycle (see Section 4.1.9).

[f] During the OLE phase, all participants will receive dual infusions of ocrelizumab 300 mg × 2 for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks. For participants randomized to the ocrelizumab group, the first infusion of ocrelizumab in the OLE phase should respect a minimum of 20 weeks from last infusion in the blinded treatment period.
For participants randomized to the placebo group, the first infusion of ocrelizumab in the OLE phase can occur once a participant meets the re-treatment criteria (see Section 6.2.3) at a scheduled visit following communication with the Sponsor.

Table 5 Overview of the Study Design and Dosing Regimen (cont.)

[g] The safety follow-up period starts after the last 24–week treatment cycle has been completed (either during the blinded treatment period or the OLE phase). Participants who withdraw from treatment will also enter the safety follow-up period. The safety follow-up period will last *up to* 48 weeks following the last infusion. *Participants who start treatment with commercial ocrelizumab or another DMT will discontinue from the study completely and will not enter the safety follow-up period.*

[h] A dose of 100 mg methylprednisolone IV and oral or IV antihistamine, such as diphenhydramine 50 mg or equivalent dose of alternative, will be administered prior to ocrelizumab or placebo infusions. In participants where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication.

Routine laboratory studies will be obtained throughout the study, with additional tests following cycles of study drug treatment. Immune panel (IgM, IgG, IgA) and serum human anti-human antibody (HAHA) tests will also be conducted. All participants will have serum samples collected for PK analysis and blood samples will be collected for CD19+ B cell counts, a PD marker of ocrelizumab. Serum, plasma and blood RNA and protein biomarker samples will be collected in consenting participants for the measurement of candidate prognostic or predictive biomarkers at baseline and selected follow-up visits (with the exception that RNA will not be collected in the OLE phase).

During the blinded treatment period: to prevent potential unblinding as a result of adverse events or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety. Each site will have 2 blinded investigators: a Principal Investigator or Treating Investigator and a Rating Investigator or Examining Investigator. The Treating Investigator is the safety assessor and should be a neurologist with experience in the care of participants with MS.
The Treating Investigator will have access to both safety and efficacy data and will make all treatment decisions based on the participant's clinical response and laboratory findings. The Examining Investigator is the efficacy assessor and should be a neurologist or other qualified health care practitioner trained and certified in administering and scoring the Functional System Scores (FSS) and Kurtzke EDSS.
The Examining Investigator will be responsible for administration of the EDSS, including the screening assessment and will only have access to EDSS data.
The Treating Investigator and the Examining Investigator will not be allowed to switch roles.

4.1.5 Rationale for Study Design

The rationale for the elements of the study design is provided below.

4.1.5.1 Rationale for Blinded Study

To minimize possible biases in the study outcome, this is a double-blinded (participant and investigator) randomized, controlled trial comparing ocrelizumab therapy with placebo. Additional features to minimize bias in outcome measurements include the following:

- A blinded assessor (Examining Investigator) will perform neurological examinations in all participants to assess the FSS/EDSS (see Section 5.11.1)
- MRI scans in all participants will be read in a blinded fashion at the central reading center
- Ocrelizumab and placebo treatment allocation remain blinded until the primary database lock for the primary analysis
- Laboratory parameters which may be unblinding to treatment assignment, such as fluorescence-activated cells orting (FACS) cell counts, including CD19+ cells, lymphocyte count, and IgM and IgG levels, are blinded in all participants, except

those meeting unblinding criteria for safety reasons, until the primary database lock for the primary analysis

4.1.5.2 Rationale for Placebo Comparator

The acceptability of placebo in PPMS trials is consistent with current standards in MS clinical trials as outlined in Section 2.2.2. The study Sponsor recognizes that a treatment period lasting 2.5–4 years poses risks to participants randomized to both placebo and an active study drug with unproven clinical effectiveness. For this reason, several study elements are employed to protect the well-being of study participants:

- The Informed Consent Form (ICF) clearly defines the duration of the study including the blinded treatment period, OLE phase, and safety follow-up period.
  The probabilities of assignment to placebo and ocrelizumab are indicated in easily understood terms in multiple sections of the ICF. No implication is made that ocrelizumab is sure to be more effective than placebo.
- A thorough medical monitoring plan will be implemented by the study Sponsor to ensure the safety of all study participants. Moreover, an independent Data Monitoring Committee (iDMC) will be instituted to further protect the well-being of participants in the study.
- In the event that participants experience confirmed disability progression persisting for 24 weeks or more, participants will need to be re-consented about the potential benefits and risks of continuing in the blinded treatment period of the study, including the risk of further disability progression. Participants will not be forcibly withdrawn from the treatment period because they could still be benefitting from therapy despite evidence for continued disease activity. In such a case, forcible withdrawal of treatment has potential to induce harm as no alternative proven therapies exist for PPMS.
- Upon withdrawal from study treatment for any reason, study participants will be recommended to stay in the study for safety follow-up but may be eligible for treatment with some alternative therapies at the discretion of and in consultation with their Treating Investigator.

4.1.5.3 Rationale for Study Population

This study will enroll participants with PPMS with an EDSS score of 3.0–6.5 and duration of disease less than 10 years if EDSS $\leq$5 or less than 15 years if EDSS $>$5.
These criteria will be implemented to recruit participants with PPMS with more disease activity and higher severity. The age range will be limited to $\leq$55 years to maximize the benefit-risk profile of ocrelizumab; it may also reduce confounding by neurological conditions prevalent in older individuals, including but not limited to microvascular disease. Subgroup analysis from Study U2786g with rituximab in participants with PPMS, Study U2786g (OLYMPUS) suggests that participants with PPMS aged 55 or less with Gd-enhancing lesions may have benefitted from anti-CD20 therapy, while also exhibiting a lower incidence of serious infections than older participants (Hawker et al. 2009).

4.1.5.4 Rationale for Study Endpoints

The proposed study endpoints are widely accepted in trials of participants with MS, including PPMS. The primary endpoint in this study is the time to confirmed disability progression as measured by a pre-specified increase in EDSS, sustained for at least 12 weeks. Other clinical endpoints will include changes in EDSS and MSFCS, MRI parameters assessing focal lesions and diffuse changes on brain imaging, and participant-reported outcomes. More information on the study efficacy endpoints is provided in Section 8.1.

4.1.5.5 Rationale for the Treatment Duration

In MS trials at least 2 years of treatment are considered adequate to show a treatment effect on disability progression. Clinical trials in progressive forms of MS may need to be longer than 2 years' duration because of heterogeneity in disability progression rates, which have at times been historically lower than anticipated resulting in inability to show a treatment effect. At the end of a fixed 96-week treatment period in Study U2786g with rituximab in PPMS, a non-significant difference was observed with 38.5% of placebo-treated participants demonstrating sustained disability progression versus 30.2% of rituximab-treated participants. It is uncertain if a longer trial duration would have demonstrated a statistically significant difference in progression rates. Most pivotal Phase III progressive MS (PPMS and SPMS) trials have employed a 3-year minimum treatment duration. Based on results from Study U2786g (OLYMPUS), the minimum 120-week treatment period duration in the current study is anticipated to adequately demonstrate a significant treatment effect. Participants enrolled at the beginning of the study will be treated and evaluated for more than 120 weeks in order to maximize the collection of efficacy and safety data in the trial. In addition, in the event that the number of disability progression events is much lower than anticipated, the blinded treatment period may be extended by additional treatment cycles to maintain statistical power to detect a treatment difference.

4.1.5.6 Rationale for the Safety Follow-Up Period

Data collected during this period will allow evaluation of the safety of B cell repletion after stopping anti-CD20 treatment, as well as the maintenance of effect or potential for a withdrawal effect.

4.1.5.7 Rationale for Open-Label Extension Phase

Upon the completion of the blinded treatment period, participants who are considered eligible and who may benefit from treatment with ocrelizumab may be offered the chance to participate in the OLE phase. The rationale for this provision is based on the very high unmet medical need in PPMS, a condition for which there are no approved therapies and for which no unapproved therapies have shown evidence of efficacy. Following the primary analysis and the positive outcome of the study, the decision by the Sponsor was to proceed with the OLE. Please see the Ocrelizumab Investigator's Brochure for more information on efficacy and safety. This will provide a longer-term safety profile for ocrelizumab.

4.1.5.8 Rationale for the Use of Methylprednisolone and Antihistamines

In order to reduce the frequency and severity of IRRs, participants will be pre-medicated with 100 mg methylprednisolone IV and an oral or IV antihistamine, such as diphenhydramine 50 mg or equivalent dose of alternative, prior to administration of ocrelizumab. Methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes before the start of an infusion. (see Section 6.4). A recent integrated analysis of participants with MS treated with ocrelizumab revealed that the addition of antihistamines to the pre-treatment with methylprednisolone decreased the incidence of IRRs by 2-fold (OCREVUS® U.S. Package Insert [USPI]). In participants where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication prior to the infusion.
In Study WA21493/ACT4422g, approximately 35% of participants with RRMS receiving 300 mg ocrelizumab on the first infusion on Day 1 experienced an infusion-associated event, and approximately 4% experienced an event with the second 300 mg infusion on Day 15. These participants were pre-medicated with corticosteroids prior to infusion, which may in part, have contributed to a lower rate of infusion events than those observed in the rituximab MS studies (U2786g, U2787g and U3264g) in which participants were not pre-medicated with corticosteroids. Administered infrequently at a low dose, methylprednisolone is not anticipated to affect the efficacy or safety outcomes of the study. Methylprednisolone (or an alternative steroid in participants where methylprednisolone is contraindicated) will be administered to participants in both treatment groups during the treatment period to maintain the treatment blinding.

4.1.6 Rationale for Dose Selection and Dosing Intervals

The blinded treatment period of this study will evaluate the safety and efficacy, compared with placebo, of two 300 mg ocrelizumab IV infusions separated by 14 days at a scheduled interval of every 24 weeks during the treatment period. Preliminary analysis from Study WA21493/ACT4422G, a Phase II study of ocrelizumab in participants with RRMS, suggests this dosing regimen should rapidly and persistently deplete peripherally circulating CD20+ B cells and potentially reduce inflammation within the CNS. In order to assure adequate initial and sustained B cell depletion, minimize potentially dose-dependent infusion-associated events particularly upon the first infusion, avoid early production of HAHA, and maintain potential for efficacy, a dual infusion of ocrelizumab is administered for all treatment cycles.

Some experts postulate a prominent role for non-antibody mediated pathogenic mechanisms of B cell function in MS. These mechanisms might include antigen presentation to and activation of pathogenic T cells, secretion of pro-inflammatory cytokines and activation of innate immune cells. These non-antibody mediated mechanisms are thought to take place within tissues, notably the lympho-reticular system and (potentially) CNS. If this hypothesis is correct, tissue B cell depletion is

perhaps more important than depletion of circulating B cells. Whether or not CNS penetration of an anti-CD20 monoclonal antibody is necessary to deplete B cells within the CNS or confer clinical efficacy in MS remains unclear.

Dosing with ocrelizumab in all participants consists of a dual IV infusion of 300 mg × 2 separated by 14 days. This regimen results in a lower amount of ocrelizumab administered upon first exposure, and it provides an opportunity for a near-term scheduled safety assessment 2 weeks after the first dose administration. In Study WA21493/ACT4422G infusion-associated adverse events, were most frequently observed with the first infusion of ocrelizumab (see also Section 4.1). These events occurred more commonly in participants receiving a 1000 mg dose on the first infusion. Rates of infusion-associated adverse events in both dose arms diminished considerably by the second infusion, a pattern also observed with studies of ocrelizumab and rituximab in participants with RA as well as rituximab in participants with MS.

The proposed re-treatment regimen consists of two 300 mg ocrelizumab IV infusions administered 14 days apart at a scheduled interval of every 24 weeks. This dual IV infusion schedule is anticipated to be well-tolerated and is consistent with the double-blinded, 24-week, primary treatment phase of the ocrelizumab RRMS Phase II trial (Study WA21493/ACT4422G) as well as other successful trials employing a B cell depleting therapeutic approach employing dual infusions with both ocrelizumab and rituximab in participants with RA and with rituximab in RRMS (Study U2787g, HERMES). Primary efficacy results from a recent Phase III trial in participants with RA (Study WA20496/ACT4394g, FEATURE) indicate that a single infusion of 400 mg did not show a significant difference from placebo in reducing signs and symptoms of RA, while a dual infusion of 200 mg ocrelizumab administered 14 days apart did show significant efficacy compared with placebo on the primary efficacy endpoint. Therefore, to maintain the potential for efficacy with ocrelizumab in PPMS, the dual-infusion treatment paradigm for anti-CD20 antibodies that has demonstrated efficacy in RA and RRMS will be used for all treatment cycles of the study.

A 24-week re-treatment interval should adequately maintain peripheral B cell depletion as observed in Study WA21493/ACT4422g and should have potential to confer a treatment benefit in participants with PPMS. A greater time interval between doses could result in a reduction or loss of efficacy. No clinical indices or biomarkers exist to reliably track the return of clinical activity in PPMS. Thus, a 24-week re-treatment interval is selected based on expected maintenance of B cell depletion and the Sponsor's clinical experience with ocrelizumab in RRMS as well as Study U2786g with rituximab in PPMS. Please see the Ocrelizumab Investigator's Brochure for more details.

4.1.7 Rationale for Switching to Single Infusions

In the studies in RMS; Study WA21092 and WA21093) and PPMS (Study WA25046), both the single and dual infusion regimens resulted in superior efficacy vs. the

comparator, as evidenced by the effects of ocrelizumab seen in a wide range of efficacy measures in the studies. There were no differences in safety outcomes between the dual and single regimens, e.g., IRRs. After the first dose (which was given as 300 mg×2 in both RMS and PPMS), the rate of IRRs was comparable between the 300 mg infusions in PPMS and the 600 mg infusions in RMS. The overall exposure (AUC over the 24–week dosing interval) was identical between 300 mg×2 in PPMS and 600 mg in RMS, as expected with an identical dose administered. Although the maximum observed concentration was obviously different between the 300 mg and 600 mg infusions, this did not impact the IRR rate. The B cell depletion pattern, as the PD marker, was also the same for both regimens. This data indicates that 300 mg×2 and 600 mg given every 24 weeks leads to consistent safety, PK, and PD outcomes, supporting that the same single dosing regimen of 600 mg every 24 weeks would be appropriate for both participants with RMS and PPMS.

4.1.8 End of Blinded Treatment Period of the Study

The end of the blinded treatment period of the study has been defined as the date at which the last data point from the last participant that is required for the primary efficacy analysis, as defined in the Statistical Analysis Plan (SAP), is received.

4.1.9 End of Study

The end of study is now defined as *31 December 2022 or up until the approval of Study MN43964 (OLERO).*

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

The Sponsor has decided to provide the opportunity to all participants to rollover and continue their treatment and/or safety follow-up under the new extension protocol.

4.2 NUMBER OF PARTICIPANTS/ASSIGNMENT TO TREATMENT GROUPS FOR THE BLINDED TREATMENT PERIOD

Approximately 630 participants will be randomized in 2 groups in a 2:1 ratio.
An independent IxRS provider will conduct randomization and hold the treatment assignment code. Participants will be stratified by region (U.S. vs. ROW) and age (≤45 vs. >45).

There will be no replacement of participants should a participant's treatment be discontinued for any reason.

4.2.1 Participant Randomization and Enrollment

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference.

To ensure accurate and timely monitoring of participant enrollment, the following procedures will be implemented:

- Participants who are candidates for enrollment into the study will be evaluated for eligibility by the investigator to ensure that the criteria given in Sections 5.2 and 5.3 have been satisfied, and that the participant is eligible for participation in this clinical study. An eligibility worksheet will be provided for this evaluation. All participants must sign the ICF prior to screening and prior to any changes to their existing medication for the purposes of enrollment into the trial.
- Eligible participants must be randomized through IxRS prior to receiving any study medication

Participants will be randomly assigned to treatment groups. Central randomization will be performed by the IxRS and will be stratified by region (U.S. vs. ROW) and age ($\leq$45 vs. $>$45).

Participant eligibility information will be provided by the investigator or the investigator's research staff to the IxRS at randomization. The participant will be randomized and assigned a unique medication number and randomization number. As confirmation, the investigator will be provided with a faxed verification of each participant's registration.

No participant may begin treatment prior to randomization and assignment of a medication number. Under no circumstances are participants who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study.

The investigators will be notified by the Sponsor if the study is placed on clinical hold and when the study is completed or closed to further participant enrollment.

4.3 CENTERS

This will be a multicenter, international study. It is anticipated that approximately 210 sites will participate.

5. STUDY POPULATION

5.1 OVERVIEW

Males and females aged 18–55 years, inclusive, who are diagnosed with PPMS in accordance with the revised McDonald criteria (Polman et al. 2005; see Appendix 1) and who meet the inclusion/exclusion criteria provided below are eligible for enrollment into the study. For the eligibility criteria for the OLE phase, see Section 5.4.

5.2 INCLUSION CRITERIA FOR BLINDED TREATMENT PERIOD

Participants must meet the following criteria to be eligible for study entry:

- Ability to provide written informed consent and to be able to follow the schedule of activities

Participants who are unable to complete exploratory assessments (e.g., electronic participant-reported outcomes [PROs]) because of physical/disease limitations will not be excluded from the study.

- Diagnosis of PPMS in accordance with the revised McDonald criteria (2005)
- Aged 18–55 years, inclusive
- EDSS at screening from 3.0–6.5 points
- Score of ≥2.0 on the FSS for the pyramidal system that is due to lower extremity findings
- Disease duration from the onset of MS symptoms:
  - Less than 15 years in participants with an EDSS at screening >5.0
  - Less than 10 years in participants with an EDSS at screening ≤5.0
- Documented history or presence at screening of at least 1 of the following laboratory findings in a CSF specimen (source documentation of laboratory results and method must be verified):
  - Elevated IgG index
  - One or more IgG oligoclonal bands detected by isoelectric focusing
- For sexually active female and male participants of reproductive potential, use of reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, is required):
  - For female participants: 2 methods of contraception throughout the trial, including the active treatment phase AND for 48 weeks after the last dose of ocrelizumab, or until her B cells have repleted, whichever is longer. For male participants: 2 methods of contraception throughout the trial, including the active treatment phase AND for 24 weeks after the last dose of ocrelizumab. Acceptable methods of contraception include 1 primary (e.g., systemic hormonal contraception or tubal ligation of the female partner, vasectomy of the male partner) AND 1 secondary barrier method (e.g., latex condoms, spermicide) OR a double-barrier method (e.g., latex condom, intrauterine device, vaginal ring or pessary plus spermicide (e.g., foam, vaginal suppository, gel, cream).
- For participants of non-reproductive potential (adherence to local requirements, if more stringent, is required):
  - Females of reproductive potential may be enrolled if post-menopausal (i.e., spontaneous amenorrhea for 12 months confirmed by an FSH level >40 mIU/mL unless the participant is receiving a hormonal therapy for her menopause or is surgically sterile [i.e., hysterectomy, complete bilateral oophorectomy])
  - Males of reproductive potential may be enrolled if they are surgically sterile (castration)

Based on local ECs or National Competent Authority feedback additional requirements to assure contraception or to confirm menopause may be required (e.g., serum estradiol compatible with post-menopause status, longer duration of amenorrhea, higher level of FSH).

5.3 EXCLUSION CRITERIA FOR BLINDED TREATMENT PERIOD

Participants who meet the following criteria will be excluded from study entry:

- History of RRMS, SPMS, or progressive RMS at screening
- Inability to complete an MRI (contraindications for MRI, include but are not restricted to, weight ≥140 kg, pacemaker, cochlear implants, 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, etc.). Participants with contraindication to Gd can be enrolled into the study but cannot receive Gd contrast dyes during their MRI scans.
- Contraindications for or intolerance to oral or IV corticosteroids, including methylprednisolone administered IV, according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents
- Known presence of other neurologic disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotrophic virus [HTLV]-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
  - History of progressive multifocal leukoencephalopathy (PML)

5.3.1 Exclusions Related to General Health

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

- Pregnancy or lactation
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal or any other significant disease that may preclude participant from participating in the study
- Congestive heart failure (New York Heart Association III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis [TB] or atypical mycobacterial disease, but excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks prior to baseline visit (Visit 2) or oral antibiotics within 2 weeks prior to baseline visit (Visit 2)
- History or known presence of recurrent or chronic infection (e.g., HIV, syphilis, TB)

Please note: in Germany, the following additional exclusion criteria apply:

- Positive anti-HIV I at screening
- Positive anti-HIV II at screening
- Positive QuantiFERON®-TB Gold test at screening

Participants with an indeterminate result are not eligible for the study unless additional testing demonstrating a negative result is provided. Thus, these participants should have either a tuberculin skin test or have the QuantiFERON-TB Gold test repeated prior to enrollment into the study. If a tuberculin skin test is performed, an induration of >6 mm is "positive" for a participant with history of Bacille Calmette-Guerin (BCG) vaccine, while an induration of >10 mm is "positive" for a participant without history of BCG vaccine.

If necessary, a QuantiFERON-TB Gold test might be complemented by additional specific diagnostic tests as per standard procedures in the country.

- History of recurrent aspiration pneumonia requiring antibiotic therapy
- History of cancer, including solid tumors and hematological malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix of the uterus that have been excised and resolved, with documented clean margins on pathology)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study

- History of alcohol or other drug abuse within 24 weeks prior to randomization
- History of or currently active primary or secondary immunodeficiency
- History or laboratory evidence of coagulation disorders

5.3.2 Exclusions Related to Medications

- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Receipt of a live vaccine within 6 weeks prior to randomization

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

5.3.3 Exclusions Related to Medications Potentially Used for the Treatment of Multiple Sclerosis

- Previous treatment with B cell-targeted therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Any previous treatment with Campath® (alemtuzumab), anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil (MMF), cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Any previous treatment with lymphocyte-trafficking blockers (e.g., natalizumab, FTY720)
- Treatment with β IFNs, glatiramer acetate, IV Ig, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to randomization

  Participants screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Participants who discontinue their current therapy for non-medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.
- Systemic corticosteroid therapy within 4 weeks prior to screening

  The screening period may be extended (but cannot exceed 8 weeks) for participants who have used systemic corticosteroids for their MS before screening. For a participant to be eligible, systemic corticosteroids should not have been administered also between screening and baseline.

5.3.4 Exclusions Related to Laboratory Findings

- Positive serum β human chorionic gonadotropin (β-hCG) measured at screening
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR] or hepatitis C virus antibody ([HepCAb]); see Section 5.13.1.1.

- Positive rapid plasma reagin (RPR) if confirmed by microhemagglutination assay (MHA-TP) or fluorescent treponemal antibody absorption (FTA-ABS) test
- CD4 count $<300/\mu L$
- Serum creatinine >1.4 mg/dL (>124 μmol/L) for females or >1.6 mg/dL ($>141\mu$mol/L) for males
- AST/SGOT or ALT/SGPT $\geq 2.0 \times$ ULN
- Platelet count $<100{,}000/\mu L$ ($<100 \times 10^9$/L)
- Hemoglobin <8.5 g/dL (<5.15 mmol/L)
- ANC $<1.5 \times 10^3/\mu L$
- Levels of serum IgG 18% below the LLN (for central laboratory IgG <4.6 g/L)
- Levels of serum IgM 8% below the LLN (for central laboratory IgM <0.37 g/L)

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

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

5.4 ELIGIBILITY CRITERIA FOR OPEN-LABEL EXTENSION PHASE

Participants who meet the following entry criteria may participate in the OLE phase:

- Completed the blinded treatment period of the trial and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab
- Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol
- Contraception requirements:
  - Female participants who are of reproductive potential and sexually active must be willing to continue use of reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, is required)
  - One primary method of contraception throughout the OLE phase and 6 months after the last dose of ocrelizumab

- Acceptable methods of contraception include 1 primary (e.g., systemic hormonal contraception or tubal ligation, vasectomy of the male partner) OR a double-barrier method (e.g., latex condom, intrauterine device, vaginal ring or pessary plus spermicide [e.g., foam, vaginal suppository, gel, cream])
- For female participants without reproductive potential:

  Women may be enrolled if post-menopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle stimulating hormone level >40 mIU/mL) unless the participant is receiving a hormonal therapy for her menopause; or surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

- Meet the re-treatment criteria with ocrelizumab (see Section 6.2.3)

5.5 CONCOMITANT MEDICATION AND TREATMENT

5.5.1 Definitions

A concomitant medication is any drug or substance taken during the study, including the screening period. Over-the-counter medications and preventative vaccines received during the study are considered concomitant medications. A concomitant procedure is any therapeutic or elective intervention (e.g., surgery, biopsy) or diagnostic evaluation (e.g., blood gas measurements, bacterial cultures) performed during the study, including the screening period.

Concomitant medications and procedures will be reported at each visit in the relevant electronic Case Report Forms (eCRFs) starting from the baseline visit (for medication and procedures taken between screening and baseline). Medications taken for the treatment of MS in the 2-year period prior to the baseline visit and medications taken for the symptoms of MS in the 3-month period prior to the baseline visit will be recorded at the baseline visit.

5.5.2 Treatment of Multiple Sclerosis and Its Symptoms

The Treating Investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may be made if appropriate for a participant's well-being in the clinical judgment of the Treating Investigator.

Therapies for MS noted in Section 5.3.3 are NOT permitted during the blinded treatment period or the OLE phase, with the exception of a short (less than 5 days) course of systemic corticosteroids for the treatment of a relapse or worsening of MS symptoms; *IV Ig is also permitted*. For participants who discontinue treatment with ocrelizumab and enter safety follow-up period, alternative treatments for their MS as judged clinically appropriate by the Treating Investigator are allowed. However, since sufficient data are not available to assess the risks associated with switching to other products, the following recommendations are given:

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

Participants who start treatment with commercial ocrelizumab (OCREVUS®) *or another DMT* will be discontinued from the study completely and will not enter or continue in the safety follow-up period.

Although anticipated to be rare in a PPMS population, participants who initially present with a PPMS phenotype can experience a relapse. Participants who experience a relapse during the treatment period may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen is recommended, 1 g methylprednisolone IV per day for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such participants should not discontinue the treatment period solely based on the occurrence of a relapse, unless the participant or investigator feels he or she has met the criteria for withdrawal (see Section 5.6).

5.5.3 Immunization

Roche has completed a randomized, open-label vaccination study in ocrelizumab-treated participants with RMS (Study BN29739). The results of this study indicate that participants being treated with ocrelizumab may have an attenuated humoral response when immunized with an inactivated vaccine. Detailed Study BN29739 results can be found in the current version of the Ocrelizumab IB.

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

The safety of immunization with live viral vaccines following ocrelizumab or rituximab therapy has not been studied. Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, BCG, typhoid, yellow fever, vaccinia, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) is not recommended within 6 weeks prior to first dosing (see Section 5.3), during ocrelizumab treatment and for as long as the participant is B cell depleted.

Participants requiring de novo hepatitis B vaccination (which involves 3 separate doses of vaccine) should have completed the course at least 6 weeks prior to the first infusion of study drug.

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

The investigator should review the participant's immunization history and vaccination status. Known dates of immunizations can be recorded on specific eCRF pages.

5.6 CRITERIA FOR PREMATURE WITHDRAWAL

Participants have the right to withdraw from the study at any time for any reason.

In the case that the participant decides to prematurely discontinue study treatment ("refuses treatment"), he/she should complete the safety follow-up period. If the participant insists on discontinuing the study, he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the participant or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the study.

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

will be recorded on the eCRF. The participant should be followed until the adverse event has resolved, if possible.

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

It is important to distinguish between "withdrawal from treatment" and "withdrawal from study". Participants who withdraw from treatment should be encouraged to remain in the study for the full duration of the safety follow-up period (*up to* 48 weeks following the last infusion).

Participants who start treatment with commercial ocrelizumab *or another DMT* will discontinue from the study completely and will not enter or continue in the safety follow-up period.

Participants must be withdrawn from treatment (regardless of whether they are in the blinded treatment period or in the OLE phase) under the following circumstances:

- Life-threatening (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion (see Sections 6.2.2, 7.1.1.3, and 7.3.1)
- Participants who demonstrate active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B (see Sections 5.13.1.1 and 7.3.1)
- Participants with PML (see Sections 7.3.1 and 7.3.4)
- Participants who decide to discontinue the treatment
- The participant's Treating Investigator decides that discontinuation of treatment is in the best clinical interest of the participant

It should be noted that upon withdrawal from the study, any untested routine samples will be destroyed. However, information already obtained from samples up until the time of withdrawal will be used.

5.6.1 Withdrawal of Subjects from the Roche Clinical Repository

Participants who give consent to provide RCR specimens have the right to withdraw their specimen from the RCR at any time for any reason. If a participant wishes to withdraw his/her consent to the testing of his/her specimen(s), the investigator must inform the Roche monitor in writing of the participant's wishes with use of the RCR Participant Withdrawal Form and enter the date of withdrawal in the participant's eCRF. A participant withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR; likewise, a participant withdrawal from the RCR does not constitute a withdrawal from the main trial.

5.6.2 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason (see Section 5.16).

5.6.3 Re-Consent Rule (In Case of Confirmed Disability Progression)

During the blinded treatment period, in the event of confirmed disability progression on EDSS sustained for 24-weeks, the benefits and risks of study treatment should be reassessed with the participant prior to any further dosing, including a discussion of treatment options available for that participant. If the participant desires to continue blinded study treatment, then participant would be re-consented. Otherwise, the participant should be discontinued from any further treatment and entered into the safety follow-up period. The result of the discussion and, when applicable, a signed renewed consent form should be included in the participant's file and the date of re-consent should be recorded in the eCRF.

Disability progression is defined as an increase of $\geq$1.0 point from the baseline EDSS when the baseline score is 5.5 or less, and $\geq$0.5 when the baseline score is more than 5.5, that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication). Sustained means that the increase is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of the progression. Investigators will be notified by the Sponsor when an EDSS score increase meets criteria for confirmed disability progression, after which re-consent to continue study treatment must be obtained.

In the OLE phase, the re-consent rule will no longer apply.

5.7 REPLACEMENT POLICY (ENSURING ADEQUATE NUMBERS OF EVALUABLE PARTICIPANTS)

5.7.1 For Participants

No participant prematurely discontinued from the study for any reason will be replaced.

5.7.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow start-up or site-activation
- Excessively slow recruitment
- Poor protocol adherence
- Sponsor's discretion (Sponsor refers to F. Hoffmann-La Roche Ltd)

5.8 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

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

A screening examination (medical history and physical examination, including vital signs height and weight and neurological examination with EDSS assessment) should be performed within 4 weeks prior to the start of the study. An ECG and laboratory tests (routine safety, pregnancy test in women of childbearing potential, FSH for menopausal status, thyroid function tests, hepatitis screening tests, Igs, RPR, HIV test, QuantiFERON-TB Gold test (Germany only) and CD4 count will also be performed. The screening period can be extended to a total period of 8 weeks in cases when a laboratory blood test or MRI scan need to be repeated for confirmation during the screening interval or for other relevant clinical, administrative, or operational reasons. Participants must fulfill all the entry criteria for participation in the study (see Section 5).

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

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

It should be stated in the medical record that the participant is participating in this clinical study.

5.9 PROCEDURES FOR ENROLLMENT OF ELIGIBLE PARTICIPANTS

Once a participant has fulfilled the entry criteria, he or she will be randomized via IxRS to one of 2 treatment groups: 300 mg × 2 of ocrelizumab or placebo.

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

The participant randomization numbers will be generated by Roche or its designee and incorporated into double-blind labeling.

The participant randomization numbers are to be allocated sequentially in the order in which the participants are enrolled according to the specification document agreed with the external randomization company/center.

Treatment with the first study drug infusion should occur within 24 hours of randomization. In exceptional cases where all baseline assessments cannot be completed within 24 hours, the first study drug infusion can be administered within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing. In particular, there should be no evidence of an ongoing infection at the time of dosing.

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

5.10 CLINICAL ASSESSMENTS AND PROCEDURES

5.10.1 Overview of Study Visits

After the screening visit, participants fulfilling the entry criteria will be scheduled for the baseline assessments within 4 weeks (Visit 2). Randomization will occur only after the participant meets all inclusion and exclusion criteria on Day 1. The schedule of activities is described in Table 1, Table 2, Table 3, and Table 4. An overall summary of the study visits is given below followed by a detailed description of efficacy and safety assessments.

5.10.1.1 Baseline Visit (Visit 2) for the Blinded Treatment Period

Most assessments for this visit should be completed on Day 1 prior to the start of study treatment (i.e., the first IV infusion of ocrelizumab or placebo). Participants will have their vital signs checked at the specified timepoints before treatment onset and during and after the infusion (see Section 5.12.1). In addition, these participants will have laboratory samples for PK (see Section 5.14) and for B cell subtyping (see Section 5.13.2) taken before and after dosing. The participant should remain in observation for at least 1 hour after the completion of the infusion is administered (see Section 6.2.1).

5.10.1.2 Subsequent Visits During the Blinded Treatment Period

There are a minimum of 5 treatment cycles, each lasting 24 weeks in duration, i.e., Cycle = baseline to Week 24; Cycle 2 = Week 24–48; Cycle 3 = Week 48–72; Cycle 4 = Week 72–96; Cycle 5 = Week 96–120. Participants enrolled earlier in the study may undergo 7 or 8 treatment cycles, contingent on the time period required to enroll the entire study. The treatment period will end when the last participant enrolled completes their fifth treatment cycle (Week 120). In the event that the anticipated number of confirmed disability progression events is not reached when the last participant enrolled completes the fifth treatment cycle, then all participants may undergo additional treatment cycles until approximately 253 confirmed disability progression events have occurred.

Two infusion visits will occur 14 days apart, every 24 weeks through the end of the blinded treatment period (i.e., Day 1 and Week 2, Weeks 24 and 26, Weeks 48 and 50, and so forth). Non-infusion visits will occur at Week 12 and at the midpoint of each treatment cycle thereafter through the end of the blinded treatment period (i.e., Weeks 36, 60, 84, and so forth). In addition, a structured telephone interview will be done on a 4-week basis between study visits from Week 8 through the end of the blinded treatment period to identify any new or worsening neurological symptoms that warrant an unscheduled visit. All efforts should be made to schedule the visits within the provided windows.

Visits should be scheduled in relation to the baseline visit (Visit 2) providing a 20–week period is maintained between the last infusion of 1 treatment cycle and the first infusion of the next treatment cycle. This applies to all treatment groups. Participants should not receive their infusions within a shorter interval. Participants who cannot receive their infusion at the visit, should be rescheduled for a delayed dosing visit (see Section 5.10.1.5).

Additional unscheduled visits for the assessment of potential relapses, new neurological symptoms or safety events may occur at any time. Starting at Week 8, all participants will be interviewed over the telephone every 4 weeks between study visits to identify and collect information on any changes in the participant's health status (including any new or worsening neurological symptoms) that warrant an unscheduled visit (see Section 5.12.4.1).

5.10.1.3 Visits During the Open-Label Extension Phase

Participants enrolled in the OLE phase will receive a dual ocrelizumab infusion (300 mg IV infusions administered 14 days apart) for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks. See Table 4 for detailed information on the assessments that will be performed during the OLE phase. All participants participating in OLE phase must continue to be eligible for re-dosing as outlined in the criteria for re-treatment with ocrelizumab (Section 6.2.3).

5.10.1.4 Visits During the Safety Follow-Up Period

Participants who discontinue treatment for any reason (including, but not limited to, withdrawal from blinded treatment, withdrawal from OLE phase, or Sponsor decision to terminate the study) will be followed up for *up to* 48 weeks after the last infusion in the safety follow-up period with visits every 12 weeks.

Participants should be encouraged to complete the safety follow-up period.

5.10.1.5 Delayed Dosing Visits and Unscheduled Non-Dosing Visits During the Blinded Treatment Period

Delayed Dosing Visits

Visits will only be used if the infusion cannot be administered at the timepoints defined in Table 2. Thus, a participant who had all assessments of a dosing visit performed, but could not receive his/her infusion, should be rescheduled for the infusion (see Section 5.10.1.2).

If the delayed infusion is the first infusion of the treatment cycle, then the visit for the second infusion should be scheduled 14 days after the delayed first infusion (±2 days). In the event any infusion needs to be delayed, a 20–week period still must be maintained between the last infusion of one treatment cycle and the first infusion of the next treatment cycle. If a longer period of time is required, then the participant should wait for the next treatment cycle before the administration of study drug.

At the delayed dosing visit, a physical examination, including vital signs and pregnancy test will be repeated and adverse events, potential relapses, and concomitant treatments recorded. Other tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted. Any additional tests or assessments that are performed as a result of investigator judgment should be documented within the unscheduled pages of the eCRF.

Unscheduled Non-Dosing Visits

Participants developing new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their preplanned scheduled study visits, and regardless of the study period (i.e., including the follow-up and monitoring periods).

Participants will undergo a physical examination, a neurological evaluation and, if judged relevant by the investigator, other tests or assessments (such as safety laboratory tests). The EDSS assessment should be performed for any suspected neurological worsening. If a relapse is suspected, the EDSS should also be performed in addition to completing the MS relapse eCRF.

For guidance on the diagnosis of PML, see Section 7.3.4.1.

5.10.1.6 Withdrawal Visits During the Blinded Treatment Period

At the moment a participant meets 1 or more of the withdrawal criteria (Section 5.6), that particular participant is regarded withdrawn from treatment. Efforts should be made to complete the respective schedule of activities as soon as possible, if necessary at an extra visit which completes the withdrawal visit.

At the termination of the study (see Section 4.1.9), the participants will discontinue ocrelizumab treatment and should move into the safety follow-up period or will receive commercial ocrelizumab (if available in that country). All participants will undergo a

complete final evaluation according to the Withdrawal from Treatment Visit in Table 4. Thereafter, all participants will be treated according to individual center practice.

Participants who withdraw from the blinded treatment period will complete all assessments as shown in Table 2 and will enter the safety follow-up period. Participants withdrawing from the OLE phase will complete all assessments as shown in Table 4 and will enter the safety follow-up period.

For participants who have withdrawn from the blinded treatment period or the OLE phase or who are not eligible for treatment with ocrelizumab, it is at the discretion of the investigator to decide on further treatment of the underlying disease.

However, since sufficient data are not available to inform risks associated with switching to other products, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine, etc.), are strongly discouraged for as long as the participant remains B cell depleted because of unknown effects on the immune system (e.g., increased risk, incidence, or severity of infection; see Section 5.5.2 for recommendations on alternative treatments for MS and Section 5.23.5 for prolongation of safety monitoring period for participants on alternative MS treatments).

Despite all efforts, participants may withdraw from the study during the safety follow-up period. Participants withdrawing from the safety follow-up period will undergo the assessments shown in Table 3.

Note: at the Withdrawal from blinded treatment period Visit, an MRI scan will be required only if not performed in the previous 4 weeks.

5.11 CLINICAL ASSESSMENTS OF EFFICACY

5.11.1 Clinical Assessments During the Blinded Treatment Period

This is an assessor blinded study. Each site will have 2 investigators:
a Principal Investigator or a Treating Investigator and an Examining Investigator or Rating Investigator.

The Treating Investigator is the physician responsible for the participant's care and should be a neurologist experienced in the care of participants with MS.
The Treating Investigator will have access to both safety (see Sections 5.12 and 5.13) and efficacy data and will make treatment decisions based on the participant's clinical response and laboratory findings.

The Examining Investigator should be a neurologist or other health care practitioner and must be trained and certified in administering the FSS and EDSS prior to study start.
The Examining Investigator will be responsible for the administration of the FSS/EDSS

and will only have access to these data. Whenever possible, the same individual should perform the examination for the full study duration.

All efforts should be made to keep the Examining Investigator blinded to the treatment assignment. Participants will be instructed not to discuss any symptoms related to the study treatment with the Examining Investigator; the Examining Investigator should remind the participant at the start of the examination. In view of the extended duration of this study, each site will identify a primary and back-up Treating and Examining Investigator. The Treating Investigator and the Examining Investigator will not be allowed to switch roles.

5.11.1.1 Assessment of Disability

Disability in MS is commonly measured by the EDSS. The EDSS will be assessed in all participants by the independent Examining Investigator at screening, baseline, and every 12 weeks (regularly scheduled visit) during the blinded treatment period of the study, during the safety follow-up period, at any unscheduled visit, and at the withdrawal from treatment and end of study visits. As noted above, additional EDSS assessments for individual participants may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.).

Disability progression is defined as an increase of $\geq$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 $\geq$0.5 when the baseline score is above 5.5. Disability progression is considered confirmed when the increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of the progression. An alternative definition of confirmed disability progression requires that the increase in EDSS be confirmed at least 24 weeks after the initial documentation of the progression. The initial event of disability progression must occur during the blinded treatment period.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus "other") rated and scored as FSS. Each FSS is an ordinal clinical rating scale ranging from 0–5 or 6. In addition, there is an ambulation score ranging from 0–12. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death).

The MSFCS consists of 3 subscales, including the 9-HPT, PASAT, and T25FWT, which provide a global quantitative estimate of MS disability progression (Fischer et al. 1999; Frohman et al. 2008;). The MSFCS should be performed by the Examining Investigator or a qualified designee who must remain blinded to the treatment assignment.

5.11.2 Brain MRI Imaging

Magnetic resonance imaging is a useful tool for monitoring CNS lesions in MS. Different MRI-derived parameters have been related to clinical activity and T1-weighted Gd-enhancing lesions or new and/or enlarging hyperintense T2 lesions have been related to relapses. It is hypothesized that changes in brain volume may reflect brain atrophy as a result of MS-related tissue loss and may thereby correlate with long-term clinical outcome in these participants.

Brain MRI scans will be obtained in all participants at baseline and at Weeks 24, 48, and 120.

Scans will be performed by trained and certified MRI technicians. The following time windows apply:

- Visit 2 (baseline): after screening visit, but at least 10 days prior to the baseline visit
- Visit 5–17 (Weeks 24–120): should be performed within a window of ±4 weeks of the scheduled visit
- In additional cycles during the blinded treatment period, an MRI should be performed annually
- In the OLE phase, MRI should be performed annually

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

The MRI will include the acquisition of scans at each timepoint with and/or without IV administered Gd contrast enhancement.

During the blinded treatment period, **MRI scans will be read by a centralized reading center for efficacy endpoints.** The centralized reading center is blinded to the treatment assignment and the reading is performed in the absence of clinical information. Further details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologist/technicians, and the procedures for the blinded analysis of the scans at the central reading center are described in a separate MRI technical manual.

During the blinded treatment period, all MRI scans will also be reviewed locally by a radiologist for safety and the MRI scan report containing only non-MS pathology will be provided to the Treating Investigator (see Section 5.11.1 for definition). At the investigational site, only the local radiologist/technician assigned to this study may have access to the MRI scans, except at baseline, when the Treating Investigator may view the MRI scan; the Treating Investigator should not review the MRI scans obtained after randomization unless a safety concern arises. In the event that the Treating Investigator

does become aware of these MRI results, this should be documented in the eCRF, indicating the reason.

Note: During the OLE phase, it is possible for the Treating Investigator to have access to MRI scans performed during the OLE phase.

5.12 SAFETY ASSESSMENTS

The Treating Investigator is the physician responsible for participant care and will have access to efficacy and safety data collected during the study. To maintain the treatment blind between ocrelizumab and placebo, some laboratory data will not be revealed to the investigator except in exceptional conditions as described in the safety plan (see Section 6.2.3).

Note: screening results of Igs (Total Ig, IgG, IgM and IgA) and CD4+ cell counts, which are required for assessment of the inclusion/exclusion criteria, will be provided to the sites.

5.12.1 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure, respiration rate and oral or auricular temperature) will be obtained at screening and at each visit thereafter, with the participant in the semi-supine position (after 5 minutes). On the dosing days, the vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or equivalent) infusion in all participants. In addition, the vital signs for participants on ocrelizumab or matching placebo should be obtained prior to the study drug infusion, then every 15 minutes (±5 minutes) for the first hour; then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion.

On non-infusion days, the vital signs may be taken at any time during the visit.

Additional vital signs readings may be taken at the discretion of the investigator in the event of an IRRs or if clinically indicated and should be recorded on the unscheduled vital signs eCRF.

Guidance for the infusions of ocrelizumab is given in Section 6.2. This section also provides guidance on the reduction of the infusion rate in the event of IRRs.

5.12.2 Electrocardiograms

A 12-lead ECG should be taken at the visits indicated in the schedule of activities (Table 1, Table 2, and Table 4). Comments generated automatically by the ECG machine should not be recorded in the eCRF unless confirmed by a physician. An ECG is also required if the participant prematurely withdraws from the study.

5.12.3 Physical Examination

A general physical examination should be performed at the screening and baseline visits, at all dosing visits during treatment, during the safety follow-up period, and at the end of follow-up. The physical examination will be recorded as "normal" or "abnormal". If abnormal, the abnormalities should be specified on the eCRF as either an adverse event or as an ongoing condition on the Medical History form. As of the baseline visit, persisting abnormalities should be stated each time the examination is performed. Diagnosis of new abnormalities or clinically significant worsening of preexisting abnormalities should be recorded as adverse events if appropriate (see Section 7.1).

5.12.4 Neurological Examination

A neurological examination will be performed at every planned and unscheduled visit. See Section 5.11.1.1.

In the presence of newly identified or worsening neurological symptoms at any given time in the study (blinded treatment period, safety follow-up period, or OLE phase), a neurological evaluation should be scheduled promptly. The Treating Investigator should assess whether the participant is experiencing:

- A relapse of MS or MS worsening. In this case, the Treating Investigator should request EDSS to be performed by the Examining Investigator (see Section 5.11.1).
- Another neurological (non-MS) disorder. In this case, an adverse event should be reported.

Study investigators will screen participants 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).

A brain MRI scan and CSF analysis may be warranted to assist in the diagnosis of PML. See Section 7.3.4.1 for guidance on the diagnosis of PML.

Participants with suspected PML, defined as a new or worsening neurological symptom which necessitates MRI and or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing (see Section 7.3.4.1). The medical responsible and Medical Monitor should be contacted by e-mail. In addition, the medical responsible should be immediately contacted by phone.

A participant with confirmed PML should be withdrawn from the study. Progressive multifocal leukoencephalopathy should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see Sections 7.2.2 and 7.2.3).

5.12.4.1 Telephone Interview for New/Worsening Neurological Symptoms

The purpose of this structured interview is to identify and collect information on any changes in the participant's health status (including new or worsening neurological symptoms) that warrant an unscheduled visit. The telephone interview will be conducted by site personnel familiar with the participant(s) every 4 weeks between the study visits during the blinded treatment period, OLE phase, and throughout the safety follow-up period.

The site will record the date of the telephone interview in the eCRF and documentation of the interview will be maintained in the participant's Study File.

See Appendix 5 for detailed information.

5.12.4.2 Assessment of Relapse

Although relapses are anticipated to be rare in the PPMS population, participants will be evaluated for relapses by the Treating Investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapses occurring between the visits.

All new or worsening neurological events compatible with MS representing a clinical relapse are to be reported in the eCRF. Participants with clinical relapses should be referred to the Examining Investigator who will assess the FSS/EDSS independently to allow confirmation as to whether or not the clinical relapse(s) meet the criteria for protocol-defined relapse(s).

To meet the criteria for a protocol-defined relapse, the relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of least 30 days. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS, or 2 points on 1 of the appropriate FSS, or 1 point on 2 or more of the appropriate FSS. The change must affect the selected FSS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory, or visual). Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: Sexual dysfunction and Fatigue.

It should be noted that all participants with new neurological symptoms defined at a visit or over the phone should be referred to the Examining Investigator unless the Treating Investigator considers the symptoms consistent with an intensification of neurological symptoms from a transient systemic infection.

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded on a pre-specified "MS relapse" eCRF; these will also be reported as adverse events (see Section 7.1.1).

5.13 LABORATORY ASSESSMENTS

5.13.1 Specific Screening Laboratory Tests for Inclusion/Exclusion

The following screening laboratory tests must be performed before including the participant into the study. Tests will be performed at a central laboratory. All screening laboratory results will be available to both sites and the Sponsor.

5.13.1.1 Hepatitis Screening and Liver Function Monitoring

Participants with recurrent or chronic infection of hepatitis B or history/presence of hepatitis C must be excluded from enrollment into the study (see Section 5.3).

In addition, hepatitis B and C serology will be performed at screening. A positive result to either HBsAg or total HBcAb associated with positive viral DNA titers as measured by PCR, or a positive result for HepCAb should result in the participant's exclusion. Participants with evidence of past resolved hepatitis B infection (i.e., positive total HBcAb associated with a negative viral DNA) can be enrolled, and will have the hepatitis B virus (HBV) DNA checked every 12 weeks. Participants in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Participants found to have a confirmed viral DNA positive test should be referred to a hepatologist for assessment immediately. These participants will not receive further infusions of ocrelizumab and will enter the safety follow-up period.

Liver function (i.e., ALT/SGPT, AST/SGOT, gamma glutamyl transferase [GGT], alkaline phosphatase, total bilirubin) should be reviewed throughout the study.
Participants developing evidence of liver dysfunction should be assessed for viral hepatitis and, if necessary, referred to a hepatologist or other appropriately qualified expert. Study drug should be withheld until the diagnosis of viral hepatitis has been excluded. Participants developing hepatitis B or C should be withdrawn from the study and should enter the safety follow-up period. Should treatment be prescribed, this will be recorded in the eCRF. Participants with viral hepatitis due to other agents, such as hepatitis A, may resume treatment after the participant's recovery.

Information relating to the risk of recurrence of hepatitis B is provided in Section 7.3.1 and information relating to hepatitis B immunization is provided in Section 5.5.3.

5.13.1.2 Other Specific Screening Tests

Further specific laboratory screening tests, listed below will be performed, and participants may be excluded based on the results of these tests, in accordance with the inclusion/exclusion criteria:

- Positive RPR for syphilis, with MHA-TP or FTA-ABS confirmation if positive

- CD4 count $<300/\mu L$
- ANC $<1.5\times10^{3}/\mu L$
- Levels of serum IgG 18% below the LLN (for central laboratory IgG <4.6 g/L)
- Levels of serum IgM 8% below the LLN (for central laboratory IgM <0.37 g/L)
- For Germany only:
  - Positive anti-HIV I at screening
  - Positive anti-HIV II at screening
  - Positive QuantiFERON-TB Gold test at screening
  - Participants with an indeterminate result are not eligible for the study unless additional testing demonstrating a negative result is provided. Thus, these participants should have either a tuberculin skin test or have the QuantiFERON–TB Gold test repeated prior to enrollment into the study. If a tuberculin skin test is performed, an induration of >6 mm is "positive" for a participant with history of BCG vaccine, while an induration of >10 mm is "positive" for a participant without history of BCG vaccine.
  - If necessary a QuantiFERON–TB Gold test might be complemented by additional specific diagnostic tests as per standard procedures in the country
- For other routine safety screening parameters please see "Exclusion related to Laboratory Findings" in Section 5.3.

5.13.2 Standard Laboratory Assessments

The following laboratory tests will be performed according to the schedule of activities. A central laboratory will be used for all assessments, with the following exceptions:

- Urinalysis and urine microscopic examination will be performed at the site (local laboratory)
- In women of childbearing potential, the urine pregnancy test will be performed on site
- HAHA will be analyzed at Genentech, Inc. a member of the Roche group, or an alternate laboratory

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

Other laboratory tests are discussed in Sections 5.14, 5.15 and 5.18.

- **Hematology:** hemoglobin, hematocrit, RBCs, WBCs (absolute and differential), ANC, and quantitative platelet count
- **Blood chemistry:** AST/SGOT, ALT/SGPT, GGT, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, calcium, phosphorus, lactic dehydrogenase, creatine phosphokinase, and triglycerides

- **Thyroid function test**: sensitive TSH and thyroid autoantibodies will be assessed at screening

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

- Total B cells ($CD19^{pos}$)
- Total T cells ($CD3^{pos}$)
- T helper cells ($CD3^{pos}$, $CD4^{pos}$)
- T_{CTL} ($CD3^{pos}$, $CD8^{pos}$)
- Natural killer cells ($CD3^{neg}$, $CD16/56^{pos}$)
- B cell subsets (e.g., memory B cells, naïve B cells, plasma cells)

- **Quantitative Immunoglobulin:** Ig levels (including Total Ig, IgG, IgM, and IgA isotypes)
- **Antibody titers:** measurement of antibody titers to common antigens (mumps, rubella, varicella, and S. pneumoniae) will be performed. This information is used to assess the effect of ocrelizumab on specific humoral immunity to bacterial and viral antigens.
- **HAHA**: serum samples will be collected for determination of antibodies against ocrelizumab (HAHA). Samples will be screened with use of an immunoassay and possibly go through other characterization assays. The HAHA analysis will be carried out at Genentech, Inc. a member of the Roche group, or an alternate laboratory. Since ocrelizumab concentrations affect the HAHA assay, the concentration of ocrelizumab in the samples will be measured to enable interpretation of the results. Therefore, 2 separate samples are needed; 1 sample for the HAHA assay and 1 sample for ocrelizumab concentration measurement (PK sample).

  As of protocol version I (v9), HAHA and concurrent PK analyses will be discontinued on the basis that immunogenicity incidence with ocrelizumab is very low ($<1\%$) with no safety risks identified, so continuous monitoring of HAHAs in this population is unnecessary. However, in any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose.
- **Urinalysis:** a urine dipstick for blood, protein, nitrite and glucose (with use of the dipsticks provided) and a microscopic examination if abnormal and applicable will be performed on site (local laboratory)
- **Pregnancy Test:** all women of childbearing potential must have regular pregnancy tests. At screening, a serum pregnancy test will be performed through the central lab. During the study treatment and safety follow-up periods, a urine pregnancy test (sensitivity of at least 25 mIU/mL β-hCG) will be performed locally at the timepoints shown in Table 1 and Table 2. On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone infusion. A positive urine pregnancy

test should be confirmed with a serum test through the central laboratory prior to any further dosing with ocrelizumab.

5.14 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected to evaluate the PK of ocrelizumab.

5.14.1 Blinded Treatment Period

Serum samples will be collected for determination of ocrelizumab concentrations 5–30 minutes prior to the methylprednisolone infusion at the timepoints detailed in the schedule of activities (see Table 1). During infusion Days 1, 15, and 505, participants will also have samples collected for PK assessment 30 minutes (±10 minutes) following the completion of the infusion of ocrelizumab/placebo, as specified in the schedule of activities.

5.14.2 Open-Label Extension Phase

Serum samples will be collected for determination of ocrelizumab concentrations as specified in the schedule of activities (see Table 4). On the infusion days in Cycle 1, 2 blood samples should be collected, 1 sample prior to the methylprednisolone infusion and the second sample 30 minutes (±10 minutes) following the completion of the ocrelizumab infusion. On non-infusion visits (Cycle 1, Week 12 and the Withdrawal from Treatment Visit), samples may be taken at any time during the visit. For all subsequent cycles after Cycle 1, only 1 PK sample shall be taken on Day 1 prior to the methylprednisolone infusion.

As of protocol version I (v9), HAHA and concurrent PK analyses will be discontinued on the basis that immunogenicity incidence with ocrelizumab is very low (<1%) with no safety risks identified, so continuous monitoring of HAHAs in this population is unnecessary. However, in any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose.

The total blood volume collected for each PK assessment will be approximately 3.5 mL. These samples will be assayed for ocrelizumab concentration with use of an enzyme-linked immunosorbent assay at Genentech, Inc. or at an alternate laboratory.

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

5.15 ROCHE CLINICAL REPOSITORY

Specimens for dynamic (non-inherited) biomarker discovery and validation will be collected from consenting participants.

These specimens will be used for research purposes to identify dynamic biomarkers that are predictive of response to ocrelizumab treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course, and outcome of PPMS and related diseases. Specimens for dynamic biomarker discovery will be single coded like any other clinical sample (labeled and tracked with use of the participant's study identification number (see Section 17).

Specimens for genetic biomarker (inherited) discovery and validation will also be collected from consenting participants.

The pharmacogenetic information gathered through the analysis of specimens in the RCR is hoped to improve participant outcomes by predicting which participants are more likely to respond to specific drug therapies, predicting which participants are susceptible to developing adverse side effects and/or predicting which participants are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable DNA variations will be double coded: a new independent code will be added to the first code to increase confidentiality and data protection (see Section 17).

The results of specimen analysis from the RCR will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

All RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will be made available for future biomarker research towards further understanding of treatment with ocrelizumab of PPMS, related diseases and adverse events and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of the RCR specimens.

5.15.1 Specimen Types

5.15.1.1 Blood for RNA Expression Profiling

Blood (2× approximately 2.5 mL collected in PAXgene vacutainers) for RNA isolation will be obtained at various timepoints as shown in Table 1. The samples may be tested with use of techniques such as a microarray profiling system and/or reverse transcriptase PCR to study the expression profile of genes known to be involved with PPMS, and any other differentially expressed genes relative to treatment response, dose response or re-treatment. For sampling procedures, storage conditions, and shipment instructions see study Sample Handling and Logistics Manual.

Note: in the OLE phase, this sample will no longer be collected.

5.15.1.2 Blood Sample for Genetic Analysis

Blood (approximately 6 mL in K_3 EDTA) for DNA isolation will be collected as shown in Table 1. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. See study Sample Handling and Logistics Manual for more details.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the electronic Case Report Form (eCRF) and/or in the clinical database.

5.15.1.3 Blood for Plasma Assays

Blood (1 approximately 6 mL sample in EDTA) for plasma isolation will be obtained at various timepoints as shown in Table 1, Table 2, Table 3, and Table 4. These samples will be used for biomarker assays which may include neurofilaments and other candidate PPMS biomarkers. For sampling procedures, storage conditions and shipment instructions see study Sample Handling and Logistics Manual.

5.16 OPTIONAL SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

If the participant provides consent (see Section 5.16.5), a collection of biosamples for the RBR will be performed at a single timepoint during the OLE phase of the study. These samples will be used for research into MS disease progression mechanisms, identification of new MS disease progression biomarkers, and development of new therapeutic agents.

5.16.1 Overview of the Roche Research Biosample Repository

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

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. Research Biosample Repository samples may be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or MS disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of MS disease biology and drug safety
- 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

5.16.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB or 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 5.16) will not be applicable at that site.

5.16.3 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 and MS disease progression or drug safety. These samples should be collected after the participant's consent and at the next possible visit during OLE phase.

- CSF
- Paired plasma samples for the CSF
- Blood *samples including leftover samples collected during the trial*

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

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

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

5.16.4 Confidentiality

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

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

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or

participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

5.16.5 Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants 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 participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

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

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

5.16.6 Withdrawal from the Research Biosample Repository

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

global_rcr-withdrawal@roche.com

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

5.16.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant 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.

5.17 PROTEIN BIOMARKER SAMPLE

Specimens for protein biomarker discovery and validation will be collected from all participants. These specimens will be used for research purposes to identify and/or verify protein biomarkers that are predictive of response to ocrelizumab treatment (in terms of dose, safety and tolerability) and will help to understand the pathogenesis, course and outcome of PPMS and related diseases. Identification of participant subgroups with increased response to therapy or increased progression rates would provide information of significant clinical value to guide treatment decisions and aid in the appropriate use of the therapy. Analyses may include, but are not limited to, interleukin-6 (Ingram et al. 2010). For sampling procedures, storage conditions and shipment instructions see study Sample Handling and Logistics Manual, which will be provided to each study site.

At Visit 2, blood specimens (approximately 6 mL blood sample in a plain tube without EDTA for serum isolation) for protein biomarker discovery and validation will be collected from all participants.

Blood specimens for protein biomarker discovery and validation will be collected from all participants as per the schedule of activities. These specimens will be stored for 5 years after the end of the study and then destroyed, unless a different regulation for storage time is in place at a given site.

5.18 CLINICAL GENOTYPING

Specific inherited DNA polymorphisms known or hypothesized to be associated with MS or ocrelizumab activity will be investigated in all participants. At Visit 2, a whole blood sample (approximately 3 mL) will be taken for DNA extraction from every participant. The DNA will be used to determine if alleles at human leukocyte antigen (HLA) class II, Fc γ receptor IIa and Fc γ receptor IIIa affect the PK, PD, efficacy or safety of ocrelizumab. Data arising from this study will be subject to the same confidentiality as the rest of the study. Genetic counseling will be provided to participants wishing to understand the clinical relevance of study results if indicated.

Polymorphisms in the Fc γ receptor IIIa have been shown to influence the degree of B cell depletion by rituximab in the treatment of participants with systemic erythromatosus (Anolik et al. 2003). Therefore, the Fc γ receptor RIIIA polymorphism at position 158 (Val/Phe) and the Fc γ receptor RIIA polymorphism at position 131 (Arg/His) will be investigated.

Genes of the major histocompatibility complex (MHC) have been associated with MS. The genes have been mapped to the HLA class II region and account for 10%–60% of the genetic risk of MS (Ramagopalana et al. 2009). Thus, haplotypes of HLA-DR and HLA-DQ will be analyzed.

The procedures for the collection, handling and shipping of clinical genotyping samples are specified in the study Sample Handling and Logistics Manual.

In the OLE phase, for participants that did not have a clinical genotyping sample collected in the blinded treatment period, an open-label clinical genotyping sample should be collected. A whole blood sample (approximately 3 mL) will be taken for DNA extraction from each participant that did not have a DNA sample assessed from the blinded treatment period. This sample is preferred to be collected at Visit 1 of the OLE phase, but if not collected at Visit 1, it may be collected at any visit during the OLE phase. For participants where a sample was already collected, no additional sample will be collected.

5.19 PLASMA AND URINE BANKING FOR JOHN CUNNINGHAM VIRUS

Long-term storage of plasma samples and urine is planned for John Cunningham virus (JCV) DNA and/or other relevant tests for JCV, independent of an occurrence of suspected PML. Plasma samples (5 mL) and urine samples (10 mL) will be collected as per the schedule of activities. As the assay of the DNA virus has not been standardized, and a correlation between viremia and onset of PML has not been established, the JCV assessments in plasma and urine will be performed if deemed necessary in the future and not on an ongoing basis. All samples collected for JCV testing will be stored for 1 year after the last participant's last visit in the study.

As of protocol version I (v9), collection of plasma and urine samples planned for JCV DNA will be discontinued. In the event that PML is suspected, an additional plasma, urine, and CSF sample should be obtained for JCV analysis (see Section 7.3.4.1). For details, please refer to the most up-to-date Laboratory Manual providing storage conditions and shipment instructions.

5.20 PARTICIPANT-REPORTED OUTCOMES

Participant-reported outcomes assessments for purposes of assessing treatment benefit (i.e., SF-36v2, MFIS) should be performed before other efficacy or safety assessments and before administration of study drug in order to minimize bias.

The SF-36 (version 2) will be measured to assess health-related quality of life. Changes from baseline will be assessed for the total score, PCS and MCS, as well as all other subscales that comprise the SF-36.

The MFIS will assess change in the level of fatigue. The MFIS is a 21-item instrument that asks participants to rate their fatigue over the past 4 weeks on a 5-point Likert scale, indicating "Never" to "Almost always." Four scores can be derived from the MFIS, including a total score as well as scores for 3 subscales: physical, cognitive, and psychosocial functioning. Changes from baseline will be calculated for the total scale scores as well as for the subscale scores.

Participant-reported outcomes data will be collected according to the protocol schedule of activities and the data will be entered into the clinical database. For all PROs, participants will complete the assessments in countries where translations of the instruments are currently available.

Participants who are unable to complete exploratory assessments (e.g., electronic participant-reported outcomes) because of physical/disease limitations will not be excluded from the study.

5.21 PHARMACOECONOMIC ASSESSMENTS

Pharmacoeconomic assessments will be included for purposes of deriving health utilities for economic modeling. The EQ-5D will be used to derive utilities for health states included in MS economic models. During the blinded treatment period, it will be administered at baseline and Weeks 48 and 120. The EQ-5D is a PRO and should be performed before any other study assessments and before administration of study drug in order to minimize bias.

Note: in the OLE phase, the EQ-5D will not be performed.

5.22 OPTIONAL EXPLORATORY SUBSTUDIES

Participants who are randomized to the main Study WA25046 protocol have the option to participate in exploratory substudies under separate protocols and upon consent and fulfillment of additional exploratory substudy protocol criteria. The OCT Exploratory Substudy is included in the main study protocol (see Section 5.22.1 and Appendix 6).

Other exploratory substudies are run under separate study protocols:

- B cell and T cell repertoires in ocrelizumab-treated participants with MS (Study BE29353)
- Brain myelin mapping to quantify demyelination and repair in MS in a Phase III trial of ocrelizumab (Study BE29340)

- Assessment of ocrelizumab treatment effects on disability of participants with MS enrolled in the Phase III Orchestra program with use of multimodal evoked potentials (mEP) and high-resolution electroencephalogram (EEG; Study BE29354)
- Substudy of brain and spinal cord MRI in participants with MS participating in the Study BE29352 (OPERA) clinical trial

Substudies will be run only at the specific assigned sites that are referred to in the substudy protocols.

5.22.1 Optical Coherence Tomography Exploratory Substudy

A Roche-sponsored, multicenter, OCT Exploratory Substudy is being conducted. Optical coherence tomography is a noninvasive imaging tool capable of measuring changes in structural architecture of the retina and retinal nerve fiber sensitively and rapidly (Frohman et al. 2008). Optical coherence tomography can be of particular interest in MS, because optic neuritis is often the pivotal event in establishing the diagnosis of MS. Optic nerve dysfunction is characterized by optic disc pallor, loss of contrast sensitivity, and visual field defects and may occur subclinically in many other participants. It is estimated that nearly 20% of all participants with MS present initially with optical neuritis, and an additional 30%–100% will have optical neuritis at some point in their disease course (Sergott et al. 2007). Optical coherence tomography outcome measures, such as RNFL thickness and macular volumes, have been shown to correlate with clinical measures of vision loss and may facilitate visualization of any process of neurodegeneration or repair as part of natural history of MS or as a consequence of neuroprotective interventions (Costello et al. 2008).

The procedures and schedule of activities are specified in the substudy protocol (Appendix 6) and Independent Review Committee Charter.

In July 2017, Roche determined that sufficient data had been obtained from the OCT substudy. During 2017 and 2018, participating participants will be discontinued from the OCT substudy but may continue in the OLE.

5.23 OPEN-LABEL EXTENSION PHASE

The first treatment cycle of the OLE phase will consist of two 300 mg IV infusions of ocrelizumab separated by 14 days. Subsequent cycles of the OLE phase will consist of single 600 mg ocrelizumab IV infusions at a scheduled interval of every 24 weeks. For participants randomized to the placebo group in the blinded treatment period, the first infusion of ocrelizumab in the OLE phase can occur once a participant meets the re-treatment criteria (see Section 5.4) at a scheduled visit following communication with the Sponsor. For participants who were in the ocrelizumab treatment arm during the blinded treatment period, a minimum of 20 weeks must be maintained between the last infusion in the blinded treatment period and the first infusion in the OLE phase.

Participants who discontinued from the blinded treatment period will be given an opportunity to enter an OLE substudy. See Appendix 8 for details.

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

5.23.1 Overview of Schedule of Activities in the Open-Label Extension Phase

Participants participating in the OLE phase will be assessed at clinical visits as per the schedule of activities (Table 4). For the description of the assessments, see Section 5.11.

The mechanisms necessary to guarantee that the blinding of the assessor is maintained are not necessary during the OLE phase. All required assessments during the OLE phase should occur as described in Section 5.11. It is recommended that the same Examining Investigator perform the assessments throughout the OLE phase.

Visits should be scheduled with respect to the date of first infusion during the OLE phase. The visit for the second infusion should be scheduled 14 days after the first infusion of OLE Cycle 1. A minimum interval of 20 weeks should be kept between the ocrelizumab second infusion of OLE Cycle 1 and the next infusion at OLE Cycle 2. A minimum of 22 weeks should occur between ocrelizumab single infusions administered from OLE Cycle 2 onwards.

In the event that an infusion is delayed, additional tests or assessments, such as routine safety laboratory tests, may be performed when the Investigator judges that they are warranted. At infusion visits, participants should remain in observation for at least 1 hour after the completion of the infusion.

Additional unscheduled visits for the assessment of potential MS relapses, new neurological symptoms, or safety events may occur at any time. Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant.

Participants with new neurological symptoms suggestive of MS relapse or MS worsening should have an EDSS performed by the Examining Investigator. Other tests/assessments may be done as appropriate.

See Section 7.3.4.1 for guidance on the diagnosis of PML.

5.23.2 Delayed Dosing Visit in the Open-Label Extension Phase

Delayed dosing visits may be scheduled if the infusion cannot be administered at the timepoints defined in the schedule of activities (Table 4). A participant who has all assessments of a dosing visit performed but cannot receive his/her infusion should be re-scheduled for the infusion.

At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted.

In unforeseen situations, if the infusion of the first treatment cycle (Day 1) is delayed, then the visit for the second infusion should be scheduled 14 days after the delayed first infusion (±5 days). In the event any subsequent infusion needs to be delayed, a minimum interval of 20 weeks between the second infusion of Cycle 1 (Week 2) and the next infusion on Cycle 2 (Week 24) is required; a minimum of 22 weeks must occur between subsequent infusions.

5.23.3 Unscheduled Visits in the Open-Label Extension Phase

Participants who develop new or worsening neurological symptoms should be seen at the investigational site as soon as possible, regardless of the dates of their preplanned, scheduled study visits. Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant as judged by the investigator.

Participants with new neurological symptoms suggestive of relapse or worsening of MS symptoms should have an EDSS performed by the Examining Investigator. Other tests/assessments may be performed as appropriate.

See Section 7.3.4.1 for guidance on the diagnosis of PML.

5.23.4 Withdrawal Visits in the Open-Label Extension Phase

When a participant meets 1 or more of the withdrawal criteria (Section 5.6), this participant is regarded as withdrawn from treatment. Participants who withdraw from ocrelizumab treatment will need to complete all assessments as shown in Table 4 and should enter the safety follow-up period.

For participants who have withdrawn from the OLE phase or who are no longer eligible for treatment with ocrelizumab, it is at the discretion of the investigator to decide on further treatment of the underlying disease.

Since sufficient data are not available to inform the risks associated with switching to other products, certain treatments for MS, such as lymphocyte-depleting agents or lymphocyte-trafficking blockers (e.g., alemtuzumab, natalizumab, fingolimod, dimethyl fumarate, cyclophosphamide, azathioprine, etc.) are strongly discouraged for as long as the participant remains B cell depleted because of unknown effects on the immune

system (e.g., increased risk, incidence, or severity of infection; see Section 5.5.2 for recommendations on alternative treatments for MS).

Participants who start treatment with commercial ocrelizumab (OCREVUS®) *or another DMT* will discontinue from the study completely and will not enter or continue in the safety follow-up period.

5.23.5 *Continued Access to Study Treatment After the End of the Study*

The Sponsor will offer continued access to Roche investigational medicinal product (IMP; ocrelizumab) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP (ocrelizumab) after completing the study if he/she decides not to rollover to the new extension study (MN43964) and if all of the following conditions are met:

- *The participant 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 participant*
- *The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

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

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

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

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 DOSE AND SCHEDULE OF OCRELIZUMAB

During the blinded treatment period, participants will be randomly assigned to either ocrelizumab 300 mg × 2 or placebo. The first IV infusion of ocrelizumab or placebo will be administered on study Day 1.

Table 6 Treatment Groups and Schedule of Study Medication during the Blinded Treatment Period

Treatment Group	Assigned Treatment	Regimen
Group A	Ocrelizumab 600 mg	2 IV infusions of ocrelizumab 300 mg separated by 14 days
Group B	Placebo	2 IV infusions of placebo separated by 14 days

During the OLE phase, all participants will receive 2 IV infusions of 300 mg ocrelizumab separated by 14 days for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab every 24 weeks.

To reduce potential IRRs, all participants will receive prophylactic treatment with 100 mg methylprednisolone, administered by slow IV infusion, and an oral or IV antihistamine (such as diphenhydramine 50 mg or equivalent dose of alternative).
The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In participants where methylprednisolone is contraindicated, corresponding doses of other IV steroids (e.g., dexamethasone) should be used as premedication (see details in Section 6.4).

6.2 PREPARATION AND ADMINISTRATION OF OCRELIZUMAB INFUSIONS

Detailed instructions for the preparation of the infusion bags containing the study drug or placebo will be provided separately.

6.2.1 Administration of the IV Infusions

Although ocrelizumab may be administered on an outpatient basis, participants may be hospitalized for observation at the discretion of the investigator (in some countries this is the standard procedure). The study drug infusions should always be administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities.

Ocrelizumab infusions should be given as a slow IV infusion. It must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to

control the infusion rate and the study drug should be infused through a dedicated line. It is important not to use evacuated glass containers (to prepare the infusion), which require vented administration sets because this causes foaming as air bubbles pass through the solution.

6.2.1.1 Preparation of Infusion

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 approximately 1.16 mg/mL. Specific instructions for the preparation of ocrelizumab are provided separately in the Dose Preparation Guidelines.

6.2.1.2 Infusion Procedures

All participants should receive pretreatment before the infusion (see Section 6.4).

6.2.1.3 Dual Infusion Cycle (Blinded Treatment Period and First Cycle of Open–Label Extension Phase)

All treatment cycles of the blinded treatment period and the first cycle of the OLE phase will consist of 2 IV infusions of 300 mg ocrelizumab administered 14 days apart. For each infusion, it is only necessary to prepare a single infusion bag (containing 300 mg of ocrelizumab). Specific instructions are provided separately in the Dose Preparation Guidelines and must be followed exactly.

Prior to the start of the infusion, please be sure that the content of the bags is at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures. Infusion should be started at a rate of 32 mL/hr. This should be escalated at the rates shown in Table 7.

Table 7 Infusions of Ocrelizumab/Placebo 300 mg

Time (Minutes)	Infusion Rate (mL/hr)	Maximum Dose per Interval (mg)	Cumulative Dose (mg)
0–30	32	18.75	18.75
31–60	65	37.5	56.25
61–90	97	56.25	112.5
91–120	129	75	187.5
121–150 [a]	194	112.5	300 [a]

[a] Infusion of 300 mg ocrelizumab should be completed at approximately 150 minutes (approximately 2.5 hours).

6.2.1.4 Single Infusion Cycle (Open-Label Extension Cycle 2 Onwards)

Cycle 2 and onwards of the OLE phase will consist of 1 IV infusion of 600 mg ocrelizumab administered on Day 1 of each cycle. For each cycle, it is necessary to

prepare a single infusion bag containing a total of 600 mg ocrelizumab.
Specific instructions for the preparation of ocrelizumab are provided separately in the Dose Preparation Guidelines and must be followed exactly. Infusion should begin at a rate of 40 mL/hr and should be escalated at the rates shown in Table 8.

Table 8 Infusion Rates for Single Infusion of Ocrelizumab 600 mg

Time (Minutes)	Infusion Rate (mL/hr)	Maximum Dose per Interval (mg)	Cumulative Dose (mg)
0–30	40	23.18	23.18
31–60	85	49.27	72.45
61–90	130	75.36	147.81
91–120	169	98.05	245.86
121–215 [a]	200	354.14 [b]	600.00

[a] Infusion of 600 mg ocrelizumab should be completed at approximately 215 minutes (approximately 3.6 hours).

[b] This last interval is approximately 95 minutes, delivering a maximum dose of 115.94 mg per 0.5 hour.

6.2.1.5 Alternative Shorter Infusion of Subsequent 600 mg Ocrelizumab Doses

If participants did not experience a serious IRR with any previous ocrelizumab infusion, a shorter (2-hour) infusion of 600 mg can be administered for subsequent doses.
The shorter infusion should be started at a rate of 100 mL/hr. This should be escalated at the rates shown in Table 9.

Table 9 Alternative Shorter Infusions of Ocrelizumab 600 mg

Time (Minutes)	Infusion Rate (mL/hr)	Maximum Dose per Interval (mg) [a]	Cumulative Dose (mg)
0–15	100	30	30
15–30	200	60	90
30–60	250	150	240
60–120 [b]	300	360	600

[a] Assumes that the infusion bag contains 600 mg ocrelizumab in 500 mL 0.9% sodium chloride. Refer to Dose Preparation Guidelines for more information.

[b] The shorter infusion of 600 mg ocrelizumab should be completed in approximately 120 minutes (2 hours).

See Section 7.3.1.1 and the current version of the Ocrelizumab IB for further details on the alternative shorter infusion option, including safety information.

Because of the possible need to vary infusion rates depending on tolerance of the infusion, the total infusion time may exceed the time stated. Unless an infusion reaction

occurs necessitating discontinuation, the entire content of infusion bags must be administered to the participant.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs IV, 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 participant may be discharged.

The prepared infusion solution of ocrelizumab is physically and chemically stable for 24 hours at 2–8°C and subsequently 8 hours at room temperature. The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2–8°C. Infusion solution must be completely administered to the participant within 32 hours of preparation (not exceeding 24 hours at 2–8°C and 8 hours at room temperature). In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded. The infusion solution must be administered with use of an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 μM). As noted above, the diluted infusion bags should be at room temperature prior to administration to the participant.

For further information, please refer to the Dose Preparation Guidelines.

6.2.2 Ocrelizumab Dose Modifications, Interruptions, and Delays

No dose modifications are foreseen.

Slowing of the infusion rate or interruption of the infusion, may be necessary in the event of an infusion reaction. In rare cases, ocrelizumab treatment may need to be discontinued. Guidance is provided below.

6.2.2.1 Handling Infusion-Related Reactions

Handling of IRRs will depend on the intensity of symptoms (see Section 7.1.1.1 for grading of intensity of IRRs).

In the event that a participant experiences a mild to moderate (CTCAE Grade 1 or 2; Appendix 4) non-allergic infusion–related event, the infusion rate should be reduced to half the rate being given at the time of onset of the event (e.g., from 50 mL/hr to 25 mL/hr or from 100 mL/hr to 50 mL/hr). Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the next closest rate on the participant's infusion schedule and the rate increments resumed.

Participants who experience a severe infusion-related event (CTCAE Grade 3) or a complex of flushing, fever, and throat pain symptoms, should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should be re-started only after all the symptoms have disappeared.

The initial infusion rate at restart should be half of the infusion rate that was in progress at the time of onset of the reaction.

Participants who experience a life-threatening infusion-related event (CTCAE Grade 4) during an infusion should have their infusion immediately stopped and should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). These participants will be withdrawn from treatment and should enter the safety follow-up period (see Section 5.10.1.4).

6.2.3 Criteria for Re-treatment with Ocrelizumab

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

- Life-threatening (CTCAE Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection (including active TB infection, either new onset or reactivation)

  Participants with active TB infection, either new onset or reactivation, must suspend ocrelizumab treatment for as long as needed to ensure full resolution of the TB infection. These participants should receive medical care in adherence with local/national requirements until complete resolution of the TB infection and should be monitored subsequently as per local medical plans. Upon resolution of the TB infection and based on individual benefit–risk assessments, these participants will have the opportunity to restart ocrelizumab treatment if it is considered beneficial for them. Otherwise, the Treating Investigator can decide to permanently stop ocrelizumab.
- ANC $< 1.5 \times 10^3/\mu L$
- CD4 cell count $< 250/\mu L$
- Hypogammaglobulinemia IgG < 3.3 g/L
- Ongoing pregnancy or breastfeeding (for female participants)

  In the event of pregnancy, the investigator must counsel the participant as to the risks of continuing with the pregnancy and the possible effects on the fetus. Given that there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the completion of pregnancy and breastfeeding. Pregnant and breastfeeding participants should continue to follow the schedule of activities for the OLE; however, no infusions of ocrelizumab will occur. If there is a concern with the ability of a pregnant or breastfeeding participant to perform all scheduled assessments, the investigator must contact the Medical Monitor for further discussion. In the OLE period of the study, restart of ocrelizumab treatment

following pregnancy and breastfeeding will be decided as a result of a thorough benefit/risk discussion between the participant and investigator.

Any critical blinded laboratory values for IgG, absolute neutrophil count and CD4 will be provided to the Treating Investigator and the Medical Monitor. Investigators notified of their participant's critical laboratory test result will be instructed to suspend further treatment with study drug until the participant can be further evaluated. A repeat laboratory test may be necessary to confirm the results. Participants with values below these critical values should not be re-treated until the re-treatment criteria are met and these laboratory values have normalized.

In addition, prior to the second infusion of each treatment cycle participants will be evaluated for the following conditions. If any of these are present prior to re-dosing, further administration of ocrelizumab should be suspended until resolved or held indefinitely:

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

6.3 FORMULATION, PACKAGING, AND LABELING

The hospital units/pharmacy will receive a study medication kit for each participant.

- **Blinded treatment period**: the study medication kit will contain 2 single-use liquid vials with ocrelizumab or placebo
- **OLE phase:** each study medication kit will contain 1 single-use vial containing 300 mg of ocrelizumab. For OLE Cycle 1, consisting of two 300 mg IV infusions, the medication kits will be dispensed 14 days apart. For OLE Cycle 2 and subsequent cycles, consisting of one 600 mg V infusion, 2 medication kits (of 300 mg ocrelizumab each) will be dispensed.

Re-supply of study medication package will be requested via the IxRS.

Ocrelizumab is manufactured as a sterile, clear, colorless, preservative-free liquid intended for dilution for IV administration.

Ocrelizumab is supplied as a liquid formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 4% (106 mM) trehalose dehydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15 cc Type I USP glass vial, fitted with a 20 mm fluoro-resin laminated stopper and an aluminum seal with a flip-off plastic cap and contains nominal 300 mg ocrelizumab. No preservative is used as each vial is designed for single use.

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.

Ocrelizumab-matching placebo is also supplied in 15 cc single-use vials. Placebo has the same composition and configuration as the drug product, but does not contain ocrelizumab. Ocrelizumab placebo solutions for IV administration are prepared by dilution of the ocrelizumab placebo into infusion bags containing 0.9% sodium chloride, using an identical procedure as for the drug product.

For reconstitution and administration of methylprednisolone, please refer to the local Prescribing Information.

6.3.1 Storage of Ocrelizumab and Placebo Vials for Infusion

Ocrelizumab and placebo vials are stable at 2–8°C (refrigerated storage). They should not be used beyond the expiration date stamped on the carton. Expiration dating may be extended during the trial; the Sponsor will provide documentation. Ocrelizumab vials should not be frozen or shaken and should be protected from direct sunlight.

The study medication labels will be produced in accordance with the local requirements. The labels will contain the study number, the medication number, the retest date, expiry date, use by date, dosing and storage instructions.

6.4 PREVENTION AND TREATMENT OF INFUSION-RELATED REACTIONS

Methylprednisolone has been shown to decrease the incidence and the severity of infusion reactions. In participants with RA treated with a similar agent, rituximab, the rate and severity of infusion reactions markedly decreased with IV corticosteroid pre-medication (Emery et al. 2006). A recent integrated analysis of participants with MS treated with ocrelizumab revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by 2–fold.

To reduce potential infusion reactions, all participants will receive prophylactic treatment with 100 mg of methylprednisolone, administered by slow IV infusion, and an oral or IV antihistamine, such as diphenhydramine 50 mg or equivalent dose of an alternative. The methylprednisolone administration is to be completed approximately 30 minutes before the start of each ocrelizumab infusion; antihistamines should be administered 30–60 minutes prior to the start of an infusion. In the rare case when the use of methylprednisolone is contraindicated for the participant, use of an equivalent dose of alternative steroid is allowed as premedication prior to the infusion.

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

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

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

Infusion-related reactions should be treated symptomatically with oral acetaminophen/paracetamol (1 g), and IM or slow IV antihistamine administration, such as diphenhydramine (25 mg to 100 mg). Acetaminophen/paracetamol and diphenhydramine dosing should be repeated as clinically indicated. Non-allergic events should be treated symptomatically as judged clinically relevant by the investigator.

In participants with CTCAE Grade 3 or higher (severe) infusion reactions with associated respiratory symptoms (stridor, wheeze or bronchospasm), additional treatment with bronchodilators may be indicated.

Section 6.2.2 details the reduction, interruption or discontinuation of the infusion in the event of an infusion reaction.

6.5 BLINDING AND UNBLINDING (FOR THE BLINDED TREATMENT PERIOD)

The Randomization List will not be available to the study centers, monitors, project statisticians, or to the project team at Roche. All individuals directly involved in this study will remain blinded to the treatment assignment of ocrelizumab or placebo only until the analysis of the primary parameter at Week 120 or, in the event additional treatment cycles are required, when approximately 253 confirmed disability progression events have occurred. Unblinding of the treatment assignment should not occur except in the case of emergency situations where the identity of the study medication is necessary for participant management in the case of a serious adverse event. In such circumstances, the site needs to contact the IxRS for unblinding.

Emergency codes should only be broken when knowledge of the treatment is essential for the further emergency management of the participant. The Principal Investigator should make every attempt to contact the Sponsor before unblinding any participant's treatment assignment, but must contact the Sponsor within one working day after the event.

Any request from the investigator for information about the ocrelizumab dose administered to study participants for another purpose must be discussed with the Sponsor.

As per regulatory reporting requirements, the Sponsor will unblind the identity of the ocrelizumab dose for all unexpected serious adverse events that are considered by the

investigator to be related to study drug as per the relevant safety reference document(s) (e.g., the Ocrelizumab Investigator's Brochure). Details of ocrelizumab-treated participants who are unblinded during the study will be included in the Clinical Study Report.

Unblinding of the treatment assignment for ongoing safety monitoring by an independent Data Monitoring Committee (iDMC) will be performed according to procedures in place to ensure integrity of the data. Further details are described in the DMC Charter (see Section 10).

In order to facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the participant until after the interim unblinding for the primary analysis.

An independent IxRS provider will conduct the participant randomization and hold the treatment assignment codes.

6.6 ASSESSMENT OF COMPLIANCE

Accountability and compliance will be assessed by maintaining adequate drug dispensing and return records. The pharmacists should keep all drug vials to measure compliance.

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

- The identification of the participant to whom the study medication was dispensed
- The date(s), quantity of the study medication dispensed

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty vials and the dispensing logs, must be available for the Monitor to conduct drug accountability.

6.7 DESTRUCTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT

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

Written documentation of destruction must contain the following:

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

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

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

7.1.1 Clinical Adverse Events

According to the International Conference of Harmonisation (ICH), an adverse event is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can, therefore, be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a (investigational) medicinal product, whether or not considered related to the medicinal (investigational) product. Preexisting conditions which worsen during a study are to be reported as adverse events.

In the eCRF, adverse events will be reported at each visit.

Clinical relapses will be recorded only on a pre-specified “MS Relapse” eCRF.

Infusion-related reactions will be recorded only on a pre-specified “Infusion-Related Reaction” eCRF.

B cell depletion is the expected outcome of ocrelizumab treatment and is not an adverse event. However, participants may be at risk for infections and particular attention should be directed toward early identification and treatment of infections. During the study, investigators are requested to promptly investigate participants reporting signs or symptoms of infection, to take appropriate specimens for identification of the pathogen and to treat infections aggressively (see Section 7.3.1). Prior to enrollment into the study, it is recommended that the Investigator review and, if warranted, update each participant’s immunizations in accordance with country medical immunization guidelines (see Section 5.5.3).

7.1.1.1 Intensity

Adverse events will be graded according to National Cancer Institute CTCAE v4 and is provided to the investigator in a separate handout entitled “Common Terminology Criteria for Adverse Events v4.0” (Appendix 4).

Adverse events not listed by the CTCAE will be graded with use of the following criteria:

- Grade 1: discomfort noticed but no disruption of normal daily activity
- Grade 2: discomfort sufficient to reduce or affect normal daily activity
- Grade 3: inability to work or perform normal daily activity
- Grade 4: represents an immediate threat to life

Any Grade 4 adverse event, either by CTCAE criteria or the additional criteria listed above, should be reported as an serious adverse event (Section 7.2.2).

7.1.1.2 Drug–Adverse Event Relationship

Relationship of the adverse event to the treatment should always be assessed by the investigator. Description of scales can be found in Appendix 2.

7.1.1.3 Serious Adverse Events (Immediately Reportable to Sponsor)

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that, at any dose, fulfils at least 1 of the following criteria:

- Is fatal (results in death; NOTE: death is an outcome, not an event)

  The term “sudden death” should only be used when the cause is of a cardiac origin as per standard definition. The terms “death” and “sudden death” are clearly distinct and must not be used interchangeably.
- Is life-threatening (NOTE: the term “life-threatening” refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- Required in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above

  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 1 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").

For a list of serious adverse drug reactions that are considered expected, refer to the current Ocrelizumab Investigator's Brochure.

The study will comply with all local regulatory requirements and will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (see Appendix 3).

7.1.1.4 Adverse Events of Special Interest (Immediately Reportable to 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 7.2.2 for reporting instructions). Company mandated adverse events of special interest include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 7.1.3.1)
- 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.

Transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

7.1.2 Treatment and Follow-Up of Adverse Events

Adverse events should be followed up until they have stabilized or have returned to baseline status (in the event of an exacerbation of a preexisting condition). This is especially important for those events where the reported causal relationship to study medication(s) is "related". If a clear explanation is established, it should be recorded on the eCRF.

If after study completion or withdrawal, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF.

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results section of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting 1 or more of the following conditions, should be recorded as a single diagnosis on the Adverse Event eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Any laboratory result abnormality fulfilling the criteria for a serious adverse event should be reported as such, in addition to being recorded as an adverse event in the eCRF.

7.1.3.1 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. 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 7.1.1) 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 a non-serious adverse event of special interest (see Section 7.1.1.3 and Section 7.1.1.4).

7.1.3.2 Follow-Up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

B cell depletion is a PD effect and is not an adverse event.

During the blinded treatment period, blinded laboratory values for IgG, ANC and CD4, which are critical will be provided to the investigator and the Medical Monitor. Investigators notified of their participant's critical laboratory test result will be instructed to suspend further treatment with study drug until the participant can be further evaluated. A repeat laboratory test may be necessary to confirm the results. Participants with values below these critical values should not be re-treated until the

re-treatment criteria are met (Section 6.2.3) and these laboratory values have normalized. During the OLE phase, these laboratory values will not be blinded.

7.2 HANDLING OF SAFETY PARAMETERS

7.2.1 Reporting of Adverse Events

All adverse events will be documented in the eCRF.

New or worsening neurological symptoms not considered MS related should be recorded on an Adverse Event eCRF and the monitor should be informed.

7.2.2 Reporting of Serious Adverse Events

7.2.2.1 Immediate Reporting Requirements to the Sponsor

Any clinical adverse event or abnormal laboratory test value that is serious (as defined in Section 7.1.1.3) and which occurs during the course of the study, regardless of the treatment group, must be reported to the Sponsor within 24 hours of the investigator becoming aware of the event (expedited reporting). In addition, for fatal and life-threatening events, the Roche Medical Monitor should be contacted immediately. Contact numbers for the Roche Medical Monitor (including afterhours cover) will be provided to the site before any participants are screened.

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

The investigator must complete the Serious Adverse Event Reporting Form in the eCRF. Relevant follow-up information should be submitted as soon as it becomes available. Only if a technical failure prevents the ability to report an serious adverse event in the eCRF, then the paper Serious Adverse Event Reporting Form provided by the Sponsor must be completed and faxed to the number provided.

Related serious adverse events MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated serious adverse events must be collected and reported during the study through the end of the safety follow-up period, which is *up to* 48 weeks after the last infusion.

Non-serious adverse events must be reported until the end of the safety follow-up period.

A death occurring during the study or information related to such occurrence which comes to the attention of the investigator during the study must be reported, whether

considered treatment-related or not; deaths will be considered unexpected in this trial and subject to emergency reporting rules (see above).

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Ocrelizumab Investigator's Brochure and that are considered by the investigator to be possibly or probably related to study drug. Some IRBs or ECs may have other specific adverse event requirements, in accordance with international and local laws and regulations, to which investigators are expected to adhere.

The following are not considered as an serious adverse event:

- Elective hospitalizations or surgical procedures that are a result of a participant's preexisting 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 eCRF.
- Hospitalization to receive trial medication such as infusions of ocrelizumab unless this is prolonged (more than 24 hours)
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone (or with another equivalent corticosteroid; see Section 5.5.2)

Of specific importance is the prompt reporting of serious infections. In particular, PML should be reported as an serious adverse event (with all available information) with immediate notification of the Medical Monitor.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in Appendix 3.

7.2.2.2 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information

Roche Medical Responsible: [redacted], *M.D.*
Mobile Telephone No.: [redacted]
E-mail: [redacted]

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

7.2.2.3 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

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

Reporting requirements will be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed. To determine reporting requirements for single adverse event cases, the Sponsor will also assess the expectedness of the event on the basis of the current Ocrelizumab Investigator's Brochure.

In principle, adverse events that are serious, related, and unexpected will be reported in an expedited manner within 15 days (non-fatal/non-life-threatening) or 7 days (fatal or life-threatening).

Only those adverse events qualifying for expedited reporting occurring in participants on active treatment will be sent in an expedited timeframe to health authorities, investigators, IRBs, and ECs. This requires unblinding of participant treatment allocation. Investigators, IRBs, and ECs will receive reports unless local regulations require that unblinded expedited reports are sent.

The DMC will review adverse events at each quarterly meeting and assess their relation to study medication based on review of aggregate unblinded safety information until the primary analysis is performed. Following unblinding, iDMC involvement in safety monitoring throughout the OLE phase is no longer needed.

7.2.3 Pregnancy and Lactation

In the OLE phase of the study, female participants should take all appropriate precautions to avoid becoming pregnant. Women of childbearing potential must use the method of contraception defined by the protocol (see Section 5.4) for the duration of the trial and for 6 months after receiving their last infusion of ocrelizumab.
Regular pregnancy tests will be performed during the study.

Reproductive toxicology studies of ocrelizumab conducted in cynomolgus monkeys are described in the Ocrelizumab Investigator's Brochure. Studies of the effect of ocrelizumab on human reproduction have not been performed. It is not known whether ocrelizumab can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. However, since IgG molecules such as ocrelizumab are known to cross the placenta, ocrelizumab may cause fetal CD20 B cell depletion.

Because pregnancy induces a natural state of immunosuppression, it is unknown whether pregnancy in combination with ocrelizumab exposure may cause a more

profound state of immunosuppression (Branch 1992). It is also unknown whether ocrelizumab is excreted in breast milk, and what effect this might have on the breastfeeding infant. However, it should be noted that Igs are found in breast milk.

Regardless of the treatment she is receiving, a female participant must be instructed to immediately inform the investigator if she becomes pregnant during the study (including the safety follow-up period). In the event of pregnancy, the investigator must counsel the participant as to the risks of continuing with the pregnancy and to the possible effects on the fetus. Given there are insufficient, well-controlled data from studies testing the use of ocrelizumab in pregnant or breastfeeding women, all infusions of ocrelizumab must be suspended until the end of pregnancy and breastfeeding.

Pregnant and breastfeeding participants should continue to follow the schedule of activities for the OLE phase; however, no infusions will occur. If there is a concern with the ability of a pregnant or breastfeeding participant to perform all scheduled assessments, or if an assessment is contraindicated during pregnancy, the investigator must contact the Medical Monitor for further discussion. Restart of ocrelizumab treatment following pregnancy and breastfeeding will be decided as a result of a thorough benefit–risk discussion between the participant and investigator.

The investigator should report all pregnancies within 24 hours to the Sponsor by means of an eCRF Pregnancy Reporting Form. The site should continue to monitor the participant's pregnancy and enter the following information in the eCRF Pregnancy Reporting Form: the outcome of the pregnancy (including spontaneous or voluntary abortions), the details of the birth, the presence or absence of birth defects or congenital abnormalities, and any other maternal or newborn complications. Babies born to mothers participating in this study should have an assessment of their lymphocyte counts and be carefully followed until these are within the normal range for the age of the infant.

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 7.2.2).

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 7.2.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

For pregnancies occurring in female participants who have been exposed to ocrelizumab at any time during pregnancy or within 6 months prior to conception, additional

pregnancy outcome information and the health status of the child will be followed until the child is 1 year of age. Data collection is voluntary only; it does not include any interventions or invasive procedures. The data will be collected on a paper Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire that will be submitted to health authorities and IRB/ECs for their approval, along with the infant data release consent form.

For more information on the Infant Health Questionnaire, please refer to the latest version of the Infant Health Questionnaire Guidance document.

7.3 WARNINGS AND PRECAUTIONS

7.3.1 Ocrelizumab

Participants should be informed of the risks associated with taking ocrelizumab. Below are listed specific major risks of which the participants should be made aware. For the most recent information regarding identified and potential risks associated with ocrelizumab, please refer to the current version of the Ocrelizumab Investigator's Brochure.

7.3.1.1 Identified Risks and Adverse Drug Reactions Associated with Ocrelizumab Use

Infusion-Related Reactions

All CD20-depleting agents administered via the IV 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 participants that IRRs can occur within 24 hours of the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to, pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia.

Participants should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR and should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

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

Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143, ENSEMBLE Plus) designed to characterize the safety profile of shorter ocrelizumab infusions in participants with RRMS, no differences were found in

the frequency and severity of IRRs associated with shorter (2-hour) infusions compared with longer (3.5-hour) conventional infusions. For further details, refer to the current version of the Ocrelizumab 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%–6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of participants with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the IFN β-1-a group (2.9%); in PPMS, the proportion of participants 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 participants with lupus and RA treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these participant populations are provided in the Ocrelizumab Investigator's Brochure.

No opportunistic infections have been reported by any participant with MS treated with ocrelizumab during the controlled period of the pivotal trials.

In interventional clinical studies, there are no reports of hepatitis B reactivation in participants with MS treated with ocrelizumab, but it had been reported in 1 participant with RA treated with ocrelizumab. Hepatitis B virus screening should be performed in all participants before initiation of treatment with ocrelizumab as per local guidelines. Participants with active HBV infection should not be treated with ocrelizumab. Participants 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. Ocrelizumab administration should be delayed for participants with active infection until the infection is resolved.

For PML, see the "Potential Risks Associated with Ocrelizumab Use" section below.

Decrease in Immunoglobulins

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

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

Based on additional participant exposure, an apparent association between sustained decrease in Igs and serious infections with ocrelizumab was observed and was most apparent for IgG. There was no difference in the pattern (type, latency, duration, outcome) of the serious infections reported in this subset of participants compared with the overall serious infections profile. In addition, risk factors for a subset of participants 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 timepoint of assessment) and is an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion is from 51 participants in Study WA21493 and indicates that the median time to B cell repletion (returned to baseline or LLN, whichever occurred first) of B cells was 72 weeks (range: 27–175 weeks).

Impaired Response to Vaccination

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

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

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

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

levels have recovered. Therefore, measuring CD19+ B cell levels in neonates and infants prior to vaccination is recommended.

The safety of immunization with live or live-attenuated viral vaccines, following ocrelizumab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended while B cells are depleted.

7.3.1.2 Potential Risks Associated with Ocrelizumab Use

Malignancies, Including Breast Cancer

An increased risk of malignancy with ocrelizumab may exist. Participants should follow standard breast cancer screening guidelines.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is an important potential risk for ocrelizumab. It has been reported in participants receiving ocrelizumab but only in participants where other contributory factors were present, such as prior immunosuppressive treatment (e.g., natalizumab or fingolimod). Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset or worsening of neurological signs or symptoms, as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for JCV DNA, and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. More information on PML can be found in Section 7.3.4. Please see the most recent Ocrelizumab Investigator's Brochure for more details regarding PML risk and see Section 7.3.4.1 for guidance on diagnosing PML.

Neutropenia

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

Hypersensitivity Reactions

No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials. Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although not typically during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during an infusion, the infusion must be stopped immediately and permanently. Participants with known IgE–mediated hypersensitivity to ocrelizumab must not be treated.

7.3.2 Corticosteroids

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

7.3.3 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 (OCREVUS USPI).

7.3.4 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a potentially fatal neurological condition linked to reactivation of a polyomavirus (JCV) and active viral replication in the brain. Polyomavirus infection is acquired in childhood and up to 80% of adults demonstrate serological evidence of past infection. Reactivation of JCV replication with transient viremia or viriuria unassociated with clinical symptoms may occur spontaneously in healthy persons. Less frequently, CNS symptoms associated with active viral replication in brain tissue is observed. The clinical syndrome is significantly more frequent among immune suppressed participants.

Physicians should consider the diagnosis of PML in any participant presenting with new 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), at each visit.

If PML is considered, a neurological consultation should be obtained and treatment suspended until PML has been ruled out. If PML is confirmed in a participant receiving ocrelizumab, no further infusions should be administered and the participant will be withdrawn from treatment (see Section 5.6). No known interventions can reliably prevent PML or adequately treat PML, if it occurs.

It is not known whether the risk of PML is altered by anti-CD20 treatment given as monotherapy. See Section 7.3.4.1 for guidance on the diagnosis of PML.

Progressive multifocal leukoencephalopathy should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor. Study drug should be withheld and participants with confirmed PML should be withdrawn from the study.

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

Detailed information regarding PML risk with ocrelizumab treatment can be found in the current Ocrelizumab Investigator's Brochure.

7.3.4.1 Guidance for Diagnosis of PML

The following diagnostic algorithm framework (see Figure 1) will be implemented in this study.

Comprehensive neurological assessments will be performed every 12 weeks at the regular study visits. Participants will be required to undergo a neurological examination for calculation of an EDSS score every 12 weeks. This requires that FSS also be determined. The examination to calculate the FSS includes cognitive, visual and motor assessments, the neurological systems most often affected by PML, as well as assessments of other neurological systems.

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

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

In addition to the neurological evaluation at regular visits, participants will undergo a telephone interview between the study visits by site personnel familiar with the participant(s). The purpose of this interview is to identify new or worsening neurological symptoms that warrant an unscheduled visit (Appendix 5). Partners or caregivers of study participants, if applicable, will be informed on symptoms and signs that may be suggestive of PML and should be instructed to contact the site, should any such signs or symptoms appear.

In the event that new or worsening neurological symptoms are considered during the telephone interview, a neurological evaluation will be conducted. Should a non-MS etiology, such as PML, be considered, further assessments should be done (see Figure 1).

The following clinical guidance is provided.

Treatment of Relapse and Other Neurological Symptoms

- As in all MS studies, new or recurrent neurological symptoms occurring in study participants should prompt careful clinical evaluation
- Given the occurrence of PML in immunocompromised participants with other anti–CD20 and MS DMTs, PML should be considered in participants who develop worsening neurological signs or symptoms
- There are no pathognomonic signs or symptoms that distinguish MS from PML, but there are certain clinical features that may help differentiate between the 2 conditions (see Table 10)

- In addition to PML and MS, other CNS conditions (e.g., stroke, migraine, etc.) should be considered when evaluating a participant with new neurological changes
- Relapses should be managed according to the study protocol
- Corticosteroid treatment should only be considered for cases in which PML is unlikely on clinical grounds and when the severity of the relapse warrants such treatment. Lack of response to corticosteroids should trigger further investigation.

Action Steps if PML is Suspected

If the clinical presentation is suggestive of PML, further investigations should include brain MRI evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 1), a lumbar puncture with evaluation of the CSF for the detection of JCV DNA should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.

Please note: in the event that PML is suspected, additional plasma, urine, as well as CSF samples should be obtained for JCV analysis. Cerebrospinal fluid samples will be analyzed, with use of a high-sensitivity test, upon receipt and the results will be provided directly to the investigational site and to the Sponsor. The additional plasma and urine samples will be stored together with the routine JCV samples. The JCV samples will be stored for 1 year after last participant, last visit. For details, refer to the most up-to-date Laboratory Manual providing storage conditions and shipment instructions.

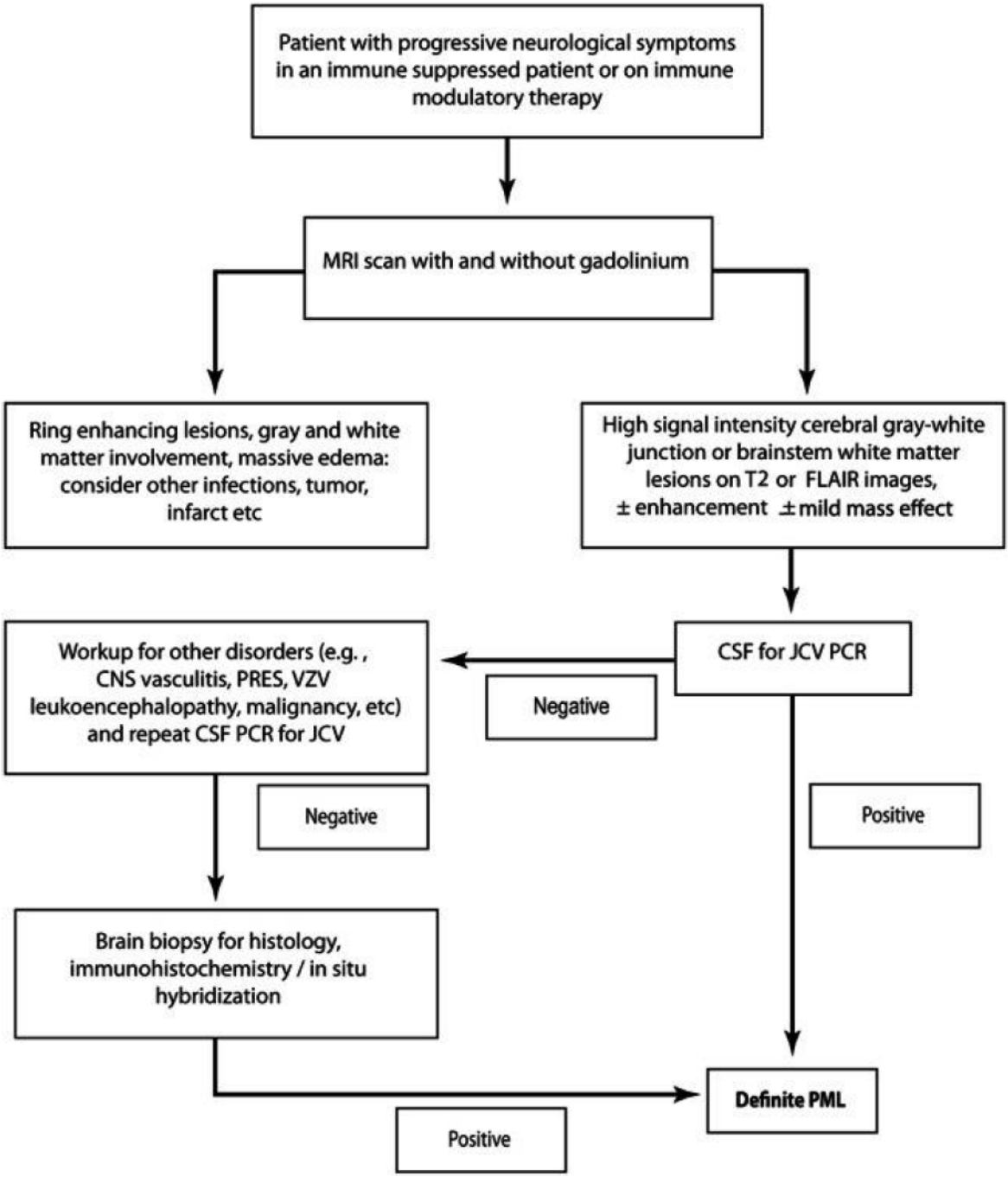
MRI Assessment

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess participants 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 11 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 participant with clinical and MRI features suggestive of PML establishes the diagnosis of PML
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis

Figure 1 Diagnostic Algorithm Framework for PML



Source: Berger et al. 2013

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

Table 10 Clinical Signs and Symptoms Typical of MS and PML

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

Source: Kappos et al. 2007.
MS =multiple sclerosis; PML =progressive multifocal leukoencephalopathy.

Table 11 MRI Lesion Characteristics Typical of MS and PML

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal cord, in white and possibly grey matter	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to grey 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 grey 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)

Table 11 MRI Lesion Characteristics Typical of MS and PML (cont.)

Feature	MS (relapse)	PML
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 participants with HIV, some peripheral enhancement is possible, especially under therapy.
Atrophy	Focal atrophy possible due to focal white matter degeneration; no progression	No focal atrophy

Source: Yousry et al. 2006.
MS =multiple sclerosis; PML =progressive multifocal leukoencephalopathy.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all statistical issues and planned statistical analyses were specified in a separate SAP, which was finalized prior to the primary database lock and unblinding of the study database. The existing SAP may be updated to describe the analyses of the OLE phase or a separate SAP will be prepared, prior to the final study database lock.

8.1 STUDY ENDPOINTS

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the time to onset of confirmed disability progression during the blinded treatment period. Disability progression is defined as an increase of ≥ 1.0 point from baseline EDSS, if the baseline EDSS is ≤ 5.5 points, or an increase of ≥ 0.5 points, if the baseline EDSS is > 5.5 points, for which change is not attributable to another etiology (e.g., fever, concurrent illness, MS relapse or exacerbation, or concomitant medication). Confirmation of disability progression must occur at a regularly scheduled visit that is at least 12 weeks after the initial disease progression. The non-confirmatory EDSS assessments (if any) between the initial and confirmation of disability progression should be at least as high as the minimum change required for progression.

8.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The time to onset of confirmed disability progression over the treatment period, defined as an increase of ≥ 1.0 point from baseline EDSS, if the baseline EDSS is ≤ 5.5 points, or an increase of ≥ 0.5 points, if the baseline EDSS is > 5.5 points, that is sustained for at least 24 weeks
- The change in T25FWT from baseline to Week 120
- The change in total volume of T2 lesions on MRI scans of the brain from baseline to Week 120
- The percentage change in total brain volume as detected by brain MRI from Week 24–120
- The change in SF-36 PCS score from baseline to Week 120
- To evaluate the safety and tolerability of ocrelizumab 300 mg $\times 2$ (over 24-week treatment cycles) compared with placebo in participants with PPMS

8.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in this study will include, but may not be limited to:

Clinical:

- The proportion of participants with confirmed 12-week disability progression at Week 120
- The change in EDSS score (mean change and AUC) from baseline to Weeks 48, 96, and 120
- The change in MSFCS score from baseline to Weeks 48, 96, and 120
- The time to confirmed disability progression over the treatment period, defined as an increase in EDSS that is sustained for at least 12 weeks (0.5 or 1 points, same criteria as for the primary endpoint time to 12-week CDP) or a 20% increase in T25FWT that is sustained for at least 12 weeks, or a 20% increase in the 9-HPT that is sustained for at least 12 weeks

- The time to sustained 20% increase in T25FWT and 9-HPT
- The proportion of participants with a 20% increase in T25FWT
- The proportion of participants with a 20% increase in 9-HPT
- The change in PASAT from baseline to Week 120

Imaging:

- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 lesions as detected by brain MRI
- The percentage change in cortical grey matter volume from baseline to Week 120
- The percentage change in white-matter volume from baseline to Week 120
- The change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain

Participant-Reported Outcomes:

- The change in fatigue, as measured by the MFIS total score and subscale scores (Physical Impact, Cognitive Impact, and Psychological Impact) from baseline to Week 120
- The change in quality of life, as measured by the SF-36 MCS score from baseline to Week 120

Biomarkers:

- To investigate the PK and other PD study endpoints of ocrelizumab
- To explore the impact of ocrelizumab therapy on biomarkers associated with the proposed inflammatory or neurodegenerative process in PPMS

OLE:

- To evaluate the long-term safety of ocrelizumab treatment during the OLE phase of the study
- To evaluate the long-term effects of ocrelizumab on clinical and MRI parameters of disease activity and progression during the OLE phase of the study

8.1.4 Safety

Safety will be assessed through regular neurologic and physical examinations, vital signs, ECG and the occurrence of adverse events, as per the schedule of activities.
In addition, the following will be examined:

- Non-MS pathology in all available MRI scans
- Complete routine hematology, chemistry and urinalyses
- Circulating B cell total and subsets, T cells, natural killer cells and other leukocytes
- Plasma Igs

- HAHA: in any case of anaphylaxis, anaphylactoid reaction, or serious or severe hypersensitivity reaction, HAHA and ocrelizumab concentration samples should be collected as close as possible to the event and then at 4 and 16 weeks postdose
- Antibody titers for mumps, rubella, varicella, and S. pneumoniae
- Serial pregnancy tests [serum/urine β-hCG) will be performed in women of childbearing potential
- JCV plasma/urine assessment only if deemed necessary

8.2 STATISTICAL AND ANALYTICAL METHODS

Prior to unblinding the treatment groups, a SAP will be produced that will contain full details of all planned analyses. An outline of the planned analyses is described below.

The primary analysis will be conducted when the blinded treatment period ends. A primary database lock will occur when the last participant has completed their Week 120 assessment. In the event an additional treatment cycle is instituted for all participants because of lower than anticipated disability progression rates at 120 weeks, then the primary database lock will occur when approximately 253 confirmed disability progression events have occurred. The treatment assignments will be unblinded to the Sponsor at this time for the purposes of data analysis. An additional analysis comprising of both safety and efficacy endpoints will be conducted at the end of the follow-up period to investigate the maintenance of the treatment effect and/or the potential for a withdrawal effect.

The primary and secondary endpoint related to confirmed disability progression will use all available data in the database at the time of the analysis. All other endpoints concerning a specific time point, e.g., change from baseline to Week 120, will only use data collected for each participant up to and including that timepoint. Any data collected for participants beyond that time point will not be included in the endpoint derivation or analysis.

All analyses, summaries and listings will be performed using SAS® software (v8.2 or higher in a UNIX environment).

8.2.1 Primary Efficacy Analysis

The primary efficacy analysis for this trial will compare the time to confirmed disability progression (12-week confirmation) between ocrelizumab and placebo.

Time to confirmed disability progression (12-week confirmation) is defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit $\geq$ 12 weeks after the initial disability progression. Disability progression is defined as an increase of $\geq$ 1.0 point from baseline EDSS, if the baseline EDSS is between 3.0–5.5 points (inclusive), or an increase of $\geq$ 0.5 points, if the baseline EDSS is $>$ 5.5 points. The assessments within 30 days after a protocol-defined relapse will not be

used for confirmation of confirmed disability progression. The non-confirmatory EDSS assessments (if any) between the initial and confirmation of disability progression should be at least as high as the minimum change required for progression.

Participants who did not have initial disability progression at time of primary database lock, time of early discontinuation, or lost to follow-up will be censored at the date of their last EDSS assessment occurring during the treatment period. Participants who had initial disability progression with no confirmatory EDSS assessment and who are on treatment at time of primary database lock will be censored at the date of their last EDSS assessment. Participants who had initial disability progression and then discontinue the treatment early with no confirmatory EDSS assessments will be considered as having confirmed disability progression.

Time to confirmed disability progression for the ocrelizumab arm and the placebo arm will be compared with use of a 2-sided log-rank test stratifying by geographic region (U.S. vs. ROW) and age ($\leq$45 vs. $>$45). The proportion of participants with confirmed disability progression will be estimated with use of Kaplan-Meier methodology. The overall hazard ratio will be estimated with use of a stratified Cox regression model with the same stratification factors used in the stratified log-rank test above.

Other sensitivity analyses may also be performed for the primary efficacy endpoint (and documented in the SAP).

8.2.2 Secondary Efficacy Analyses

Each secondary efficacy endpoint will be tested in the hierarchical order listed here, if the primary endpoint and each preceding endpoint have reached the significance level of 0.05.

8.2.2.1 Time to Onset of Confirmed Disability Progression Confirmed for $\geq$24 Weeks

Time to confirmed disability progression over the treatment period, defined as an increase of $\geq$1.0 point from baseline EDSS if the baseline EDSS is $\leq$5.5 points, or an increase of $\geq$0.5 points if the baseline EDSS is $>$5.5 points, that is sustained for 24 weeks.

A secondary efficacy analysis for EDSS-based disability progression in this trial will compare the time to confirmed disability progression between ocrelizumab and placebo using a 24-week confirmation window for disability progression. The analysis of EDSS progression will be conducted as described for the primary analysis with the exception that the time to confirmed disability progression (24-week confirmation) is defined as the time from baseline to the first disability progression, which is confirmed at the next regularly scheduled visit $\geq$24 weeks ($\geq$161 days) after the initial disability progression. The same analysis principles as described in Section 8.2.1 will be applied to the 24–week confirmed disability endpoint.

8.2.2.2 Change in Timed 25-Foot Walk Test from Baseline to Week 120

For the assessment of differences in the mean change in the T25FWT from baseline up to Week 120, a Mixed-Effect Model Repeated Measures (MMRM) analysis will be performed.

8.2.2.3 Change in Total Volume of T2 Lesions on MRI Scans of the Brain from Baseline to Week 120

For the assessment of differences in the mean change in total volume of T2 lesions from baseline up to Week 120, an MMRM analysis will be performed.

8.2.2.4 Percent Change on MRI from Week 24 to Week 120 in Total Brain Volume

For the assessment of differences in the percent change in total volume of T2 lesions from baseline up to Week 120, an MMRM analysis will be performed.

8.2.2.5 Change from Baseline in Quality of Life as Measured by the SF-36 (Physical Component Summary)

For the assessment of differences in the mean change in PCS score from baseline to Week 120, an MMRM analysis will be performed.

8.2.3 Exploratory Analyses

The exploratory endpoints will be summarized with use of tables, listings and graphs, where appropriate. Full details of the derivations and analyses of exploratory endpoints will be provided in the SAP.

8.2.4 Sample Size

The sample size was estimated on the basis of data from a rituximab Phase II/III trial in adults with PPMS (Study U2786g). For the current study, the 2-year progression rate among participants receiving ocrelizumab is predicted to be 30%, as compared with 43% among participants receiving placebo. A 2-group test of equal exponential survival with exponential dropout is used to determine the sample size for the time to confirmed disability progression. With a 2:1 randomization ratio between the ocrelizumab and placebo arms and the assumption of a 1-year accrual period with a 3.5-year maximum treatment period, the total sample size of 630 participants provides approximately 80% power, maintaining the type I error rate of 0.01 (or approximately 92% power for Type I error rate of 0.05), and assuming a dropout rate of 20% over 2 years.

8.2.5 Hypothesis Testing

The null hypothesis will be tested at $\alpha = 0.05$ level (2-sided test). The hypotheses to be tested are as follows:

- H_0 (null hypothesis): there is no difference in the time to confirmed disability progression between the ocrelizumab and placebo groups
- H_1 (alternative hypothesis): there is a difference in the time to confirmed disability progression between the ocrelizumab and placebo groups

Time to confirmed disability progression for the ocrelizumab group and the placebo group will be compared with use of a 2-sided log-rank test stratifying by geographic region (U.S. vs. ROW) and age ($\leq$45 vs. $>$45). If the test result is statistically significant at $\alpha < 0.05$ level (2-sided test), we will conclude that the ocrelizumab arm demonstrated a superior effect of increasing time to confirmed disability progression of participants, when compared with the placebo arm.

Similar hypotheses will also be tested for the secondary efficacy parameters. Methods for handling multiplicity issues related to secondary endpoints will be described in the SAP.

8.2.6 Analysis Populations

One participant population will be defined for the purpose of the safety analysis and two for the efficacy analysis. All efficacy analyses will be performed with use of the intent-to-treat (ITT) population. The per protocol (PP) population will be used for the primary and some secondary efficacy analyses in order to evaluate the influence of major protocol violators and as a sensitivity check to the ITT analysis.

8.2.6.1 Safety Population

This population will be used for all summaries of safety data. The safety population will include all participants who received any study drug. Randomized participants that receive incorrect therapy from that intended will be summarized in the group according to the therapy actually received. Participants who are not randomized, but who receive study drug will be included in the safety population and summarized according to the therapy actually received.

8.2.6.2 Intent-to-Treat Population

All randomized participants will be included in the intent–to-treat population. Participants who prematurely withdraw from the study for any reason and for whom an assessment is not performed for whatever reason will still be included in the ITT analysis. Participants who receive an incorrect therapy from that which is intended will be summarized according to their randomized treatment.

8.2.6.3 Per Protocol Population

The PP population will include all participants in the ITT population adhering to the protocol. Participants may be excluded if they significantly violate the inclusion/exclusion criteria or deviate from the study plan. Specific reasons for warranting exclusion will be agreed and documented in the SAP prior to unblinding of the treatment groups. Only those participants with violations that are deemed to potentially affect the efficacy of study treatment will be excluded from the PP population. Participants who receive an incorrect therapy from that intended will be excluded from the PP population.

8.2.7 Interim Analysis

No formal efficacy interim analyses are planned.

8.2.8 Safety Data Analysis

All safety parameters will be summarized and presented in tables based on the safety population. Randomized participants that receive incorrect therapy from that intended will be summarized in the group according to the therapy actually received. Participants who are not randomized, but who receive study drug will be included in the safety population and summarized according to the therapy actually received.

The safety data will be listed and summarized at determined cut off points, e.g., at the time of the primary analysis with use of all safety data available, after the 120-week visit for each participant, and at the end of follow-up period with use of all safety data available.

All adverse events will be coded and tabulated by System Organ Class and Preferred Term for individual events within each body system, and will be presented in descending frequency. Adverse events will also be tabulated by severity and relationship to the study medication. Serious adverse events will be summarized separately.

Associated laboratory parameters such as hepatic function, renal function and hematology values will be grouped and presented together. Marked abnormalities will also be flagged. Marked abnormalities will be tabulated for each laboratory test by treatment group.

Analysis of HAHA to ocrelizumab will be summarized graphically and descriptively. Correlation between presence of HAHA and IRR/anaphylactic reactions/B cell depletion will be presented descriptively.

The change from baseline for each of the vital sign variables will be computed and included in individual participant listings and summarized with use of descriptive statistics.

Physical examination and ECG data will be summarized descriptively and presented in individual participant listings.

An external, iDMC will review safety data throughout the study and will convene at least 3 × per year. After the primary unblinding, iDMC involvement in safety monitoring throughout the OLE phase is no longer needed. Analyses required for the DMC data review will be performed as described in the DMC Charter and DMC data handling plan.

8.2.9 Safety Follow-Up Period

Data from this period will be analyzed to provide information on the maintenance effect and the potential withdrawal effect of ocrelizumab. In addition, data will be analyzed to provide information concerning the long-term safety of ocrelizumab. Data will be summarized and tables and listings will be produced.

8.2.10 Open-Label Extension Phase

Data from this period of the study will be analyzed in order to characterize the long-term safety and efficacy of ocrelizumab beyond the blinded treatment period of the study. The data will be summarized according to the randomized treatment groups of the blinded treatment period of the study. Details of the statistical analyses will be provided in the SAP.

8.2.11 Other Analyses

8.2.11.1 Pharmacokinetic Analysis

Pharmacokinetic Parameters

Ocrelizumab serum concentration-time data will be modeled with use of a population approach. The primary population PK parameters (clearances and volumes) for ocrelizumab will be estimated by means of nonlinear mixed-effects modeling (NONMEM) analysis of the sparse PK data. Clearances with associated inter-participant variability may be characterized by a saturable and non-saturable clearance as well as an intercompartmental clearance depending on the final structural model. Volumes with associated inter-participant variability may be characterized by central and peripheral volumes depending on the final structural model. Exposure (AUC) to ocrelizumab will be estimated. The selection of other parameters will depend on the final PK model used for this analysis.

Pharmacokinetic Analysis

Nonlinear mixed-effects modeling (with software NONMEM [Beal et al. 1992]) will be used to analyze the sparse sampling dose-concentration-time data of ocrelizumab. Participants who have measurable concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation. The PK data of this study may be pooled with more extensive data from other studies. Population PK parameters (clearances and volumes) will be estimated and the influence of covariates, such as age, sex, weight, HAHA, and baseline CD19 lymphocytes, on these parameters will be investigated.

Details of the mixed-effects modeling analyses will be described in a Modeling and Simulation Analysis Plan and results will be reported separately.

8.2.11.2 Pharmacodynamic Analysis

If possible, nonlinear mixed-effects modeling (with software NONMEM [Beal et al. 1992]) will be used to investigate the relationship between ocrelizumab exposure and the safety

and efficacy parameters, which may, include but are not limited to, the proportion of participants with confirmed disability progression, number of Gd-enhancing T1 lesions on brain MRI scans, and volume and number of T2 lesions on brain MRI scans. Classical hierarchical PK-PD models like linear, E_{max} or sigmoidal E_{max} models will be used. The possibility of a delay between the time-course of effects and exposure will be investigated with use of indirect PD models. Time to event and logistic regression analyses will also be conducted when appropriate.

Exploratory analyses may be performed to assess the possible relationship between PD markers, PK and clinical response.

8.2.11.3 Biomarker Sample Repository/Biomarker Research Samples

Additional blood samples for serum and/or plasma analyses and CSF (CSF for RBR only) will be taken for research purposes subject to discretionary approval from each center's IRB/EC and the participant's specific written consent. These samples will be used to identify dynamic biomarkers to help us better understand the pathogenesis of PPMS and response to treatment with ocrelizumab. Such future biomarkers have yet to be determined but may include circulating biochemical markers in blood, including cytokines as well as peripheral blood gene expression patterns. Exploratory statistical data analyses may include assessments for possible relationships between these biomarker levels, PK and clinical response.

8.2.11.4 Clinical Genotyping

DNA analysis will be performed only on baseline samples (collected during the blinded treatment period and the OLE phase) clearly designated for this purpose.
These samples will only be used for investigation involving PPMS and ocrelizumab response, and will not be used to determine genetic susceptibility to diseases that participants do not currently have.

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

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

Data for this study will be recorded via an Electronic Data Capture (EDC) system with use of electronic Case Report Forms. It will be transcribed by the site from the paper source documents onto the eCRF (in no case is the eCRF to be considered as source data for this trial). In addition, EDSS, MSFCS, and PROs will be collected according to the protocol schedule of activities, and the data will be entered into the clinical database.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug dispensing log by the investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the data base will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.

Throughout the study the Study Management Team will review data according to the Data Validation Manual.

In order for the Sponsor to make recommendations or decisions regarding further development of the drug, it may open the blinding code as soon as the adverse event and primary data for a group have been transcribed onto the eCRF and the clinical scientist and investigator have reviewed the data.

In order to facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the subject until the database is closed.

9.1 ASSIGNMENT OF PREFERRED TERMS AND ORIGINAL TERMINOLOGY

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, with use of the most up-to-date version of the MedDRA terminology for adverse events, diseases and medical history and the International Non-proprietary Name Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. STUDY COMMITTEES

10.1 STEERING COMMITTEE

An external Steering Committee will provide general guidance, assist with liaison to investigators and oversee any external communication of the results of the study.

10.2 DATA MONITORING COMMITTEE

An external iDMC will be chartered to review safety data and make recommendations regarding continuation, termination, or modification of the study. Regularly scheduled safety data reviews will occur approximately on a quarterly basis after the first participant is enrolled. A full review for safety will be performed after all participants have completed the first treatment cycle. After the primary unblinding, iDMC involvement in safety monitoring throughout the OLE phase is no longer needed.

Any safety event that requires unblinding will be immediately reported to the DMC and to the health authorities in an expedited safety report. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary

to ensure the safety of participants. The safety evaluations will be conducted on parameters specified within the DMC Charter and may vary depending on the requirements and requests of the DMC. Besides the conventional safety variables, such as serious adverse events, laboratory tests, and vital sign changes, results of B cell counts, IRRs, thromboses, infections, and HAHA rates, will be carefully examined. In addition, one MRI measurement (the total number of gadolinium-enhancing T1 lesions) will be evaluated to monitor for any worsening (safety MRI parameter).

The details of the DMC roles and responsibilities and the logistics of the DMC activities will be outlined in a DMC Charter. The purpose of the DMC interim analyses is primarily safety evaluation, and the study may be stopped or amended because of significant safety concerns.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 LOCAL REGULATIONS/DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the E.U./EEA countries, the investigator will ensure compliance with the E.U. Clinical Trial Directive [2001/20/EC]. For studies conducted in the U.S. or under U.S. IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, Subchapter D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

In other countries where a "Guideline for Good Clinical Practice" exists, Roche and the investigators will strictly ensure adherence to the stated provisions.

12.2 INFORMED CONSENT

Written informed consent from participants:

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain signed informed consent from each participant prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For the participant not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the participant and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the participant and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the participants are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The eCRFs for this study contain a section for documenting participant informed consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit–risk assessment, the consent form should be reviewed and updated if necessary. All participants (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

12.3 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

Ethics committees [non-U.S.] for EEA member states, the Sponsor or its deputy/representative will submit to the Competent Authority and ECs the protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the study used to obtain informed consent as well as any advertising or compensation given to the participant).

Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the EC's approval must be re-submitted by the investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

Institutional Review Board [U.S.]: it is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an IRB. This board must operate in accordance with the current Federal Regulations. The Sponsor will receive a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments/modifications are made to the protocol.

Sampling for the RCR and RBR is contingent on review and approval for the exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site's IRB/EC. If a regulatory or site's IRB/EC does not approve the sampling for the exploratory assessments the section on biomarker sampling will not be applicable.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the investigator (investigator representative[s] in the case of a multicenter trial).
Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the Clinical Science Leader/Clinical Pharmacologist and Biostatistician.

All protocol modifications must be submitted to the appropriate IRB or EC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except

for changes necessary to eliminate an immediate hazard to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]).

14. CONDITIONS FOR TERMINATING THE STUDY

Both the Sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

15. STUDY DOCUMENTATION, ELECTRONIC CRFS, AND RECORD KEEPING

15.1 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 different separate categories (1) Investigator's Study File, and (2) participant clinical source documents.

The investigator's Study File will contain the protocol/amendments and schedule of activities, IRB/EC and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition, at the end of the study the investigator will receive the participant data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the investigator's Study File.

Participant clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include participant hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and participant screening and enrollment logs.

The investigator must keep these 2 categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the

investigator and Roche to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit.
Where source documents are required for the continued care of the participant, appropriate copies should be made for storing outside of the site.

15.2 SOURCE DOCUMENTS AND BACKGROUND DATA

The investigator shall supply the Sponsor on request with any required background data from the study 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 subject confidentiality is protected.

15.3 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit or its designees, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection and as per the monitoring plan established in the study.

15.4 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an EDC system, which will be accessed via the Web. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change.

For each participant enrolled, an eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the study staff. This also applies to records for those participants who fail to complete the study. If a participant withdraws from the study, the reason must be noted on the eCRF. If a participant is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

It is understood that the responsible Roche monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (eCRFs and other pertinent data) provided that participant confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and

accuracy of the data being entered on them. The monitor must verify that the participant received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by IxRS). The monitor should have access to laboratory test reports and other participant records needed to verify the entries on the eCRF. The investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche Clinical Repository specimens will at all times be tracked in a manner consistent with Good Clinical Practice, by a quality-controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the study protocol and ICF, respectively. Roche monitors and auditors will have direct access to appropriate parts of records relating to participants participating in this study for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to source data and documents related to the RCR Research Project.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PARTICIPANT RECORDS

The investigator must assure that participants' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, participants should not be identified by their names, but by an identification code. The investigator should keep a Participant Identification Log showing codes, names and addresses. The investigator should maintain documents not for submission to the Sponsor, e.g., participants' written consent forms, in strict confidence.

Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e., assigning a unique participant ID number at the investigator site) all participants enrolled in Roche clinical studies. This means that participant names are not included in data sets that are transmitted to any Roche location. Given the sensitive nature of genetic data, Roche has implemented a number of additional processes to assure participant confidentiality. All specimens taken for inherited genetic research that will be stored in the RCR (see Section 5.15) undergo a second level of "coding". At Roche, the specimen is transferred to a new tube and labeled with a new random number. This is referred to as "Double Coding (De-Identification)". Data generated following the use of these specimens and all clinical data transferred from the clinical study database and considered relevant, will also be labeled with this same code. The "linking key" between the participant's identification number and this new independent code will be stored in a secure database system. Access to the table linking the participant identification number to the specimen code will be strictly limited and monitored by audit trail. Legitimate operational reasons for accessing the "linking key" will be documented in a standard operating procedure. Access to the

"linking key" for any other reason will require written approval from the Governance Committee responsible for the specimen(s).

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants 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 participants 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 (ICMJE) authorship requirements. Any formal publication of the study in which input of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Data derived from RCR specimen analysis on individual participants will not be provided to study investigators, except where explicitly stipulated in a study protocol (e.g., if the result is an enrollment criterion). Exceptions may be granted (e.g., if biomarker data would be linked to safety issues). The aggregate results of any research conducted with use of RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Appendix 1
Revised McDonald Criteria 2005

Table 3. Diagnosis of Multiple Sclerosis in Disease with Progression from Onset

Original McDonald Criteria	2005 Revisions
1. Positive CSF *and* 2. Dissemination in *space* by MRI evidence of nine or more T2 brain lesions *or* Two or more cord lesions *or* Four to eight brain lesions and one cord lesion *or* Positive VEP with four to eight MRI lesions *or* Positive VEP with less than four brain lesions plus one cord lesion *and* 3. Dissemination in *time* by MRI *or* Continued progression for 1 year	1. One year of disease progression (retrospectively or prospectively determined) 2. *Plus* two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF[a] (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both).

[a]MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues[20] and Tintoré and coworkers[21] as presented in Table 2.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; VEP = visual-evoked potential.

REFERENCE

Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–6.

Appendix 2
Adverse Event Categories for Determining Relationship to Test Drug

The causality relationship of study drug to the adverse event will be assessed by the investigator as either: Yes or No.

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as Yes.

The following criteria should be considered in order to assess the relationship as Yes:

- Reasonable temporal association with drug administration
- It may or may not have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as No:

- It does not follow a reasonable temporal sequence from administration of the drug
- It may readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant
- It does not follow a known pattern of response to the suspected drug
- It does not reappear or worsen when the drug is readministered

Appendix 3
ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least 1 of the following criteria:

- Is fatal (results in death)
  NOTE: death is an outcome, not an event.
- Is life-threatening
  NOTE: the term "life-threatening" refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected adverse event is one in which the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For serious adverse events, possible causes of the event are indicated by selecting 1 or more options (check all that apply):

- Preexisting/Underlying disease – specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness) – specify

The term severe is a measure of intensity, thus a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the Adverse Event eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the IRB/EC of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

24-HOUR MEDICAL COVERAGE

Identification of a contact for 24-Hour Medical Coverage is mandatory to be compliant with worldwide regulatory agencies and to ensure the safety of study participants.

An Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Roche medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours 7 days a week. Toll-free numbers will be distributed to all investigators running Roche Pharma Development clinical trials. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular Clinical Science Leader cannot be reached.

Appendix 4
Common Terminology Criteria for Adverse Events

In the present study, toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

The CTCAE v4 can be found in the Roche handout entitled: "Common Terminology Criteria for Adverse Events v4.0" or on the following Web site: https://ctep.cancer.gov.

Appendix 5
Telephone Interview

The purpose of this interview is to identify and collect information on any changes in the participant's health status (including new or worsening neurological symptoms) that warrant an unscheduled visit.

The telephone interview will be conducted by site personnel familiar with the participant(s) every 4 weeks between the study visits.

The date of the telephone interview will be recorded in the eCRF.

The use of this form is optional, but if not used, all information should be recorded in the participant's medical records. Where used, this form should be kept with the participant's records.

Please ask the following questions during the telephone interview:

Read aloud and record participant's answers to the following questions:

Questions	No	Yes
1. Since your last visit or telephone interview, have you had any new or worsening medical problems (such as sudden changes in your thinking, alterations in your behavior, visual disturbances, extremity weakness, limb coordination problems, or gait abnormalities) that have persisted more than 1 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 or pregnancy of the partner of a male participant), surgery, or hospitalization?		
4. Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat cancer or MS, any other new medicines that weaken your immune system, or steroid medicines other than for the treatment of a recent relapse)?		

If the participant answered YES to any question, contact the investigator and review the participant's answers. The investigator can determine if an unscheduled visit is required.

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

_____

_____

_____

Name and date of staff completing the telephone interview:

NAME:_____ Date:_____

Below is a sample list of medications that can weaken the immune system:

Examples of Immunosuppressants, Antineoplastics, and Immunomodulators

Approved MS Therapies (approved in at least 1 country):

- Glatiramer acetate (Copaxone®)
- Interferon beta-1a (Rebif®, AVONEX®)
- Interferon beta-1b (Betaseron®)
- Mitoxantrone (Novantrone®)
- Natalizumab (Tysabri®)
- Fingolimod (Gilenya®)
- Alemtuzumab (Lemtrada®)
- Teriflunomide (Aubagio®)
- Dimethyl fumarate (Tecfidera®)

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®)
- Efalizumab (Raptiva®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Intravenous immunoglobulin (IVIG)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan/MabThera®)
- Trastuzumab (Herceptin®)

This list does not include all drugs that can suppress the immune system.

Participants should notify the study team of any new medications taken during the course of the study.

Appendix 6
Optical Coherence Tomography Exploratory Substudy

INTRODUCTION

Optical coherence tomography (OCT) is a noninvasive imaging tool capable of sensitive, reproducible and rapid measurements of structural architecture of the retina and retinal nerve fiber layer (RNFL; Frohman et al. 2008). Optical coherence tomography can be of particular interest in multiple sclerosis (MS), because optic neuritis often the pivotal event in establishing the diagnosis of MS. Optic nerve dysfunction is characterized by optic disc pallor and loss of contrast sensitivity, and visual field defects, which may occur subclinically in many participants. It is estimated that nearly 20% of all participants with MS present initially with optic neuritis, and an additional 30%–100% will have optic neuritis at some point in their disease course (Sergott et al. 2007). Optical coherence tomography outcome measures such as RNFL thickness and macular volumes have been shown to correlate with clinical measures of vision loss and may facilitate visualization of any process of neurodegeneration or repair as part of natural history of MS or as a consequence of neuroprotective interventions (Costello et al. 2008).

This substudy is part of 3 ongoing Phase III studies that serve to evaluate the neuroprotective effect of ocrelizumab in MS as measured by RNFL thickness and macular volume in both eyes of participants who participate in the confirmatory pivotal studies in participants with relapsing multiple sclerosis (RMS; Studies WA21092 and WA21093) or participants with primary progressive MS (PPMS; Study WA25046).

In July 2017, Roche determined that sufficient data had been collected from the OCT substudy. During 2017 and 2018, participating patients will be discontinued from the OCT substudy but may continue in the OLE.

OBJECTIVES

EFFICACY OBJECTIVES

The primary efficacy objectives for this substudy are as follows:

- To evaluate the neuroprotective effect of ocrelizumab therapy as measured by macular volume and RNFL over time
- To characterize the time-course of changes in RNFL that imply axonal loss in participants with both RMS and PPMS with or without ocrelizumab treatment

The secondary efficacy objectives for this study are as follows:

- In the case of RMS participants (Studies WA21092 and WA21093), the study will assess whether ocrelizumab 300 mg × 2 has superior neuroprotective effect compared with Rebif as measured by RNFL thickness

- In the case of PPMS participants (Study WA25046), the study will assess whether ocrelizumab 300 mg × 2 has superior neuroprotective effect compared with placebo as measured by RNFL thickness

SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the ophthalmological safety of ocrelizumab therapy in participants with MS, focusing on serious adverse events

EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate if OCT outcomes can serve as a reliable and predictive measure of response to ocrelizumab therapy in participants with MS or progression to a more severe disease state
- To evaluate the relationship of OCT outcomes with outcomes from ocrelizumab Phase III pivotal studies, such as
  - Change in brain volume as measured by brain magnetic resonance imaging (MRI)
  - Confirmed disability progression
  - T2 lesion volume
  - Number of T1 gadolinium-enhanced lesions
- Change in Multiple Sclerosis Functional Composite Scale (MSFCS) score

STUDY DESIGN

DESCRIPTION OF STUDY

Overview

The current substudy is an add-on, multicenter, longitudinal study to the ongoing Phase III ocrelizumab Studies WA21092, WA21093, and WA25046 to evaluate the neuroprotective effects of ocrelizumab treatment as measured by OCT.
Optical coherence tomography will be performed in parallel to the ocrelizumab pivotal Phase III studies. Participants will have OCT assessments as long as they are taking part in the main study for at least 1 year.

Participants can be enrolled at any time during the first 48 weeks after enrollment in the main pivotal studies. However, all attempts should be made to enroll the participant at the time of screening of the main pivotal study. Participants will undergo an ophthalmological examination prior to first OCT scan and at the end of the study. Participants will also undergo at least 3 OCT scans at 24-week intervals (see schedule of activities of this substudy; Appendix 7).

For participants participating in Study WA25046:

- The participant should undergo OCT measurements every 24 weeks after the first OCT Visit (Visit 1 of the OCT substudy). If the participant is enrolled into the OCT substudy at baseline of the main study, the following visits should occur: Visit 1 (baseline, occurring at the baseline visit of the main study), Visit 2 (Week 24, occurring at Visit 5 of the main study), Visit 3 (Week 48, occurring at Visit 8 of the main study), Visit 4 (Week 72, occurring at Visit 11 of the main study), Visit 5 (Week 96, occurring at Visit 14 of the main study), and Visit 6 (Week 120, occurring at Visit 17 of the main study).. If the participant is enrolled after baseline of the main study, OCT visits should occur every 24 weeks after the first OCT Visit (Visit 1, baseline).

For participants participating in Studies WA21092 and WA21093:

- The participant should undergo OCT measurements every 24 weeks after the first OCT Visit (Visit 1 of the OCT substudy). If the participant is enrolled into the OCT substudy at baseline of the main study, the following visits should occur: Visit 1 (baseline, occurring at the baseline visit of the main study), Visit 2 (Week 24, occurring at Visit 5 of the main study), Visit 3 (Week 48, occurring at Visit 7 of the main study), Visit 4 (Week 72, occurring at Visit 9 of the main study) and Visit 5 (Week 96; occurring at Visit 11 of the main study). If the participant is enrolled after baseline of the main study, OCT visits should occur every 24 weeks after the first OCT Visit (Visit 1, baseline).

If the participant is withdrawn from study treatment in the main protocol, an OCT Visit should occur if it has not been performed during the previous 4 weeks.
Participants should then have an OCT measurement at the end of the safety follow-up of the main protocol.

If a participant decides to participate in the OLE phase of the main protocol, OCT measurements should continue to occur every 24 weeks during the OLE phase.

A schedule of activities is provided in Appendix 7 of this substudy.

IMAGE REVIEW

A masked, central OCT reading center will review and analyze OCT images.
The procedures will be detailed in an Imaging Review Charter.

END OF STUDY

In July 2017, Roche determined that sufficient data had been collected from the OCT substudy. During 2017 and 2018, participating participants will be discontinued from the OCT substudy but may continue in the OLE.

OUTCOME MEASURES

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Overall and quadrant RNFL thickness measured by OCT
- Macular volume maps as measured by OCT

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of ophthalmological adverse events

MATERIALS AND METHODS

PARTICIPANTS

Adult participants who fulfill eligibility criteria for one of the main Phase III ocrelizumab pivotal studies (i.e., WA21092, WA21093, or WA25046) and the eligibility criteria outlined in the following inclusion and exclusion sections of this substudy can be enrolled into the study.

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Able and willing to provide written informed consent and comply with the study protocol
- Be a participant in 1 of the following studies: WA21092, WA21093, or WA25046

Exclusion Criteria

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

- Medical history of macular degeneration, retinopathy, glaucoma, amblyopia, diabetes, or any other documented cause of vision loss
- Inability to undergo reliable OCT testing
- More than 48 weeks have lapsed since randomization

STUDY ASSESSMENTS

Screening and Baseline Examination and Eligibility Screening Form

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

Consenting participants must also have signed the informed consent and be eligible for the main pivotal Phase III study. Participants will receive an ophthalmological and eye examination to be evaluated for eligibility to participate in this substudy. If the participant is eligible, this ophthalmological examination will be considered the baseline ophthalmological measure (OCT Visit 1).

It should be stated in the medical record that the participant is participating in this clinical study.

Once a participant has fulfilled all eligibility criteria, he or she will undergo OCT according to schedule of activities (Appendix 7).

Procedure in Case of Delayed Dosing Visit, Relapse or Unscheduled Visits, and Withdrawal Visits in the Main Phase III Ocrelizumab Pivotal Studies

The main ocrelizumab pivotal studies have mechanisms set up regarding delayed dosing visits, unscheduled visits due to relapse, and withdrawal visits.

Optical coherence tomography measurements should occur at initially scheduled times and should not be rescheduled due to delayed dosing schedule or unscheduled visit due to relapse. In case there is a relapse during an OCT schedule visit, the investigator should document all ocular symptoms, including ocular neuritis, in the electronic Case Report Form as well as communicate them to the Principal Investigator of the main study. If a participant suffers a relapse with symptoms acute optic neuritis during the month before OCT study, a second OCT must be performed 1 month later to account for the effect of papilledema.

If the participant is withdrawn from study treatment in the main protocol, an OCT Visit should occur if it has not been performed during the previous 4 weeks.
Participants should then have an OCT measurement every 24 weeks until the end of the safety follow-up of the main protocol.

Description of Study Assessments

Medical History and Demographic Data

Medical history and demographic data will be captured in main study in which the participant is enrolled. Further medical history includes clinically significant diseases that may cause vision loss of the affected eye that have been documented by the ophthalmologist.

Ophthalmological and Eye Examination

The presence of any visual abnormalities will be established in a full eye examination. This will include an examination performed by an ophthalmologist during screening and at the end of the study. This will include best corrected visual acuity evaluation (with Early Treatment Diabetic Retinopathy Study standardized eye chart); color vision test (Hardy Rand Rittler pseudoisochromatic plate); visual field measurement; intraocular pressure; slitlamp examination to examine the anterior parts (cornea, lens, and sclera); and a dilated ophthalmoscopic examination of retina, optic nerve, retinal blood vessels, and macula. The eye chart chosen for a participant must be consistently used throughout the study as well as the use of corrective lenses during the ophthalmological exam.

Visual Evoked Potential

Visual evoked potential (VEP) is a sensitive test of visual pathway function and a marker of optic nerve involvement in MS, and it has been used as a diagnostic tool for RMS and PPMS (Polman et al. 2005). It can be used to supplement information provided by a clinical examination to provide objective evidence of a second lesion provided that the only clinically expressed lesion did not affect the visual pathways. The VEP measurement should occur during OCT Visit 1. If available at the center, multifocal VEP will be performed instead of full-field VEP.

Note: in the rare cases that the selected site cannot deliver VEP data for any reason, VEP measurements will not be necessary after discussion with the Sponsor. However, all efforts should be made to collect VEP data during Visit 1 (baseline).

Optical Coherence Tomography

Optical coherence tomography images will be acquired in all participants as detailed in the schedule of activities (Appendix 7). In addition, an OCT scan will be performed in participants withdrawn from the main study treatment if it has not been performed within the previous 4 weeks.

All OCT images will be performed by certified personnel. The following time windows apply:

- OCT Visit 1 should occur prior to baseline visit of the primary study and at Weeks 24, 48, and 96
- In case the participant is enrolled after the baseline visit of main study, OCT Visit 1 should occur at time of enrollment into the substudy. All further OCT scans should occur every 24 weeks thereafter.

During OCT Visit 1, the OCT scan should be performed twice in order to control for test-retest reliability.

Optical coherence tomography images will be read by a centralized reading center. The reading will be performed in a masked fashion in the absence of clinical information. Further details on the OCT protocols and standardization of machines are described in a separate Imaging Review Charter.

Procedure in Case of Ocular Neuritis or Relapse

If the participant presents with optic neuritis, the affected eye should be documented. The participant should also be referred to the Principal Investigator of the main study for examination. If the participant suffers a relapse with symptoms of acute optic neuritis during the month before an OCT scan, a second OCT scan must be performed 1 month later to account for the effect of papilledema.

ASSESSMENT OF SAFETY

SAFETY PLAN

Any adverse event regarding ocular findings should be reported to the Principal Investigator of the main study in which the subject is participating, as well as the Sponsor. See main protocol Section 7 regarding the procedures related to reporting of adverse events and serious adverse events.

STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical analyses will be specified in the Independent Review Charter charter.

SAMPLE SIZE

A total of approximately 300 participants will be enrolled in this substudy, and the total study duration will be approximately 96 weeks, depending on the time of enrollment.

EFFICACY ANALYSES

The purpose of this study is to estimate the neuroprotective effect of ocrelizumab treatment in participants with MS relative to Rebif® in the case of Studies WA21092 and WA21093 and relative to placebo in the case of Study WA25046. Point and interval estimates of the decrease of RNFL thickness and macular volume will be obtained.

PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the decrease in RNFL thickness over time during the duration of the main study.

SECONDARY AND EXPLORATORY EFFICACY ENDPOINTS

Secondary and exploratory endpoints are:

- Determination of macular volume over time during the duration of the study
- Exploratory correlation analyses to determine the predictive value of OCT measures (RNFL thickness and macular volume) with outcomes measured in the main study, such as (but not restricted to):
  - Change in brain volume as measured by brain MRI
  - Confirmed disability progression
  - T2 lesion volume
  - Number of T1 gadolinium-enhanced lesions
- Change in MSFCS score

SAFETY ANALYSES

No safety analyses are planned for this substudy. Any safety event noted during this substudy will be forward to the Principal Investigator of the main study. See Section 7 of the main protocol.

REFERENCES

Costello F, Hodge W, Pan YI, et al. Tracking retinal nerve fiber layer loss after optic neuritis: a prospective study using optical coherence tomography. Mult Scler 2008;14:893–905.

Frohman, EM, Fujimoto JG, Frohman TC, et al. Optical coherence tomography: a window into the mechanisms of multiple sclerosis. Nat Clin Prac 2008;4:664–75.

Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–6.

Sergott RC, Frohman E, Glanzman R, et al. The role of optical coherence tomography in multiple sclerosis: expert panel consensus. J Neurol Sci 2007;263:3–14.

Appendix 7 Optical Coherence Tomography Exploratory Substudy Schedule of Activities

	Blinded Treatment Period [a]							Open-Label Extension Phase (WA25046) [c] (± 14)	Completion/ Early Termination Visit	Safety Follow-Up	Withdrawal Visit
Week (window in days)	0	24 (± 14)	48 (± 14)	72 (± 14)	96 (± 14)	120 (± 14)	Additional Cycles [b] (± 14)				
Informed consent	x										
Ophthalmological medical history and baseline conditions	x										
OCT [d]	x	x	x	x	x	x	x	x	x	x [e]	x
Adverse events [f]	x	x	x	x	x	x	x	x	x	x	x

OCT = optical coherence tomography; OLE = open-label extension.

[a] Treatment period is variable, as it depends on the time of enrollment within the main study.

[b] Participants who continue with additional cycles of the blinded treatment should have OCT assessments every 24 weeks.

[c] If a participant enrolls in the OLE phase of the main study, OCT assessments should occur every 24 weeks.

[d] In cases where the initially submitted OCT Visit scan is inadequate/not evaluable by Bern Photographic Reading Center, the site should make all efforts to request the participant to come back to site to perform a new OCT scan.

[e] Safety follow-up: OCT assessment should continue every 24 weeks counting after last OCT assessment visit.

[f] Any adverse events should be reported to the Principal Investigator of the study.

Appendix 8
Open-Label Extension Substudy in Participants Who Discontinued Treatment in the Blinded Phase of Study WA25046

BACKGROUND AND RATIONALE FOR THE SUBSTUDY

In the absence of prior proof-of-concept clinical data with ocrelizumab in PPMS, Study WA25046 was designed to introduce the open-label extension (OLE) phase only if a positive benefit–risk of ocrelizumab was determined by the Sponsor after the primary analysis of the blinded period.

The primary analysis of the blinded treatment period in Q3 2015 showed that the study met its primary endpoint and key secondary endpoints, and a decision was made by the Sponsor to initiate the OLE phase.

The main protocol excludes participants from the OLE if they withdrew early from the blinded treatment period. The substudy described here allows these participants the opportunity of entering the substudy OLE if they meet eligibility criteria for the purposes of collecting further safety data.

The substudy protocol was designed because these participants who withdrew early are confounded by a time gap in which they did not receive any treatment at all or received treatment with drugs other than ocrelizumab. Therefore, the data from these participants will need to be analyzed separately from those participants who transitioned directly from the blinded treatment period into the OLE without a gap. As opposed to participants who completed the blinded treatment period and who can transition into OLE directly, the participants who withdrew from blinded treatment early will need to go through a screening step before they are allowed to enter OLE.

SUBSTUDY OBJECTIVES

The same objectives apply to this OLE substudy as for the OLE period described in the main protocol (Section 3).

SUBSTUDY DESIGN

DESCRIPTION OF STUDY PERIODS

This substudy consists of the following study periods: a screening period, an OLE treatment period, and a safety follow-up period.

- Screening period: up to 4 weeks
- OLE treatment period: participants will be receiving open-label ocrelizumab. The same conditions apply to the duration of the OLE phase in this substudy as for the participants entering OLE through the main protocol (Section 4.1).
- Safety follow-up period: the safety follow-up period will begin when the participant completes or discontinues from OLE phase for any reason. The same conditions

apply to the duration of the safety follow-up Period in this substudy as for the participants entering OLE through the main protocol (Section 4.1).

END OF SUBSTUDY

The end of the substudy is the same as the end of the main Study WA25046 (protocol Section 4.1.9).

NUMBER OF PARTICIPANTS

Participants who withdrew early from the blinded treatment period of Study WA25046 for any reason are given an option to enter screening for participation in this OLE substudy, except those participants who discontinued due to hypersensitivity to ocrelizumab if it manifested as a Grade 4 infusion-related reaction (IRR). Participants will be allowed to enroll in this substudy up to 24 months after communication from Sponsor.

STUDY POPULATION

Participants who fulfill the eligibility criteria outlined in the following inclusion and exclusion sections of this substudy protocol can be enrolled into the study.

INCLUSION CRITERIA

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

- Having received at least 1 dose (2 infusions separated by 2 weeks) of blinded study drug (either placebo or ocrelizumab) in the blinded treatment period of Study WA25046
- Having withdrawn early from treatment during the blinded treatment period of Study WA25046 for any reason, with the exception of those participants who discontinued due to hypersensitivity to ocrelizumab if it manifested as a Grade 4 IRR; both participants who entered the safety follow-up and participants who withdrew from study are eligible
- Participants whose EDSS at screening is >6.5 are eligible if in the judgment of the investigator and following discussion with the participant, the benefit–risk of ocrelizumab treatment is considered acceptable
- Willing to use appropriate contraceptive methods as described in Section 5.4 of the main protocol
- Ability to provide written informed consent and to be able to follow the schedule of activities of the substudy

EXCLUSION CRITERIA

Participants who at the time of screening for substudy entry meet any of the following criteria will not be allowed to enter the substudy:

Exclusions Inherited from the Blinded Treatment Period of WA25046

- Meeting any of the general exclusion criteria of the blinded treatment phase listed in Section 5.3 of the main protocol

- Meeting any of the 'exclusion criteria related to general health' listed in Section 5.3.1 of the main protocol
- Meeting any of the 'exclusion criteria related to medications' listed in Section 5.3.2 of the main protocol

Exclusions Related to Laboratory Findings

- Positive serum β human chorionic gonadotropin (β-hCG) measured at screening
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive total hepatitis B core antibody [HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C virus antibody (HepCAb; see Section 5.13.1.1
- Positive rapid plasma reagin (RPR) if confirmed by microhemagglutination assay (MHA-TP) or fluorescent treponemal antibody absorption (FTA-ABS) test
- CD4 count $<250/\mu L$
- ANC $<1.5\times10^3/\mu L$
- Levels of serum IgG 18% below the LLN (for central laboratory IgG <3.3 g/L)

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

Exclusions Related to Medications Potentially Used for the Treatment of Multiple Sclerosis

- Any previous treatment with these B cell–targeted therapies: atacicept, belimumab, or ofatumumab
- Treatment with rituximab if the last infusion is within 22 weeks prior to screening
- Any previous treatment with Campath® (alemtuzumab), anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil (MMF), cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Treatment with fingolimod or other S1P receptor modulator (e.g., siponimod) within 12 weeks prior to screening
  NB: only participants with T lymphocyte count $\geq$LLN will be eligible for this study.
- Treatment with natalizumab within 24 months prior to infusion
  NB: participants previously treated with natalizumab will be eligible for this study only if duration of treatment with natalizumab was <1 year.
- Treatment with teriflunomide of dimethyl fumarate (BG12) within 12 weeks prior to screening

- Treatment with IV immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 12 weeks prior to screening; treatment with IFN-β or glatiramer acetate is allowed until screening

  Participants screened for this substudy should not be withdrawn from therapies for the sole purpose of meeting eligibility for the substudy.

- Systemic corticosteroid therapy within 4 weeks prior to screening

  The screening period may be extended (but cannot exceed 8 weeks) for participants who have used systemic corticosteroids for their MS before screening. For a participant to be eligible, systemic corticosteroids should not have been administered also between screening and baseline.

SCHEDULE OF ACTIVITIES AND PROCEDURES

Schedule of activities in this substudy will be identical to that of participants entering OLE through the main protocol (Table 4 of Section 1.2 of main protocol), with the exception of screening period that is inserted specifically for this substudy before the OLE treatment phase.

See Table 1 for the schedule of activities for screening period, OLE treatment phase, delayed dosing visit, Unscheduled visit, and Withdrawal from Treatment Visit.

For the safety follow-up period, the same provisions apply as for the participants entering OLE through the main protocol. See Table 3 of Section 1.2 of the main protocol for schedule of activities during safety follow-up period.

Appendix 8 **Open-Label Extension Substudy in Participants Who Discontinued Treatment in the Blinded Phase of Study WA25046 (Cont.)**

Table A8-1 Substudy Schedule of Activities

		Substudy Open-Label Treatment Phase (Identical To Main Study OLE) [a, b]							Delayed Dosing Visit [d]	Unscheduled Visit [e]	Withdrawal from Treatment Visit
Cycle	Unique To Substudy	1			2		N [c]				
Visit		D1	D15	w12	D1	w12					
Week in OLE Phase (window in days)	Screening −28 to −1	0 (±5)	2 (±5)	12 (±7)	24 (±5)	36 (±7)	n (±5)	n + 12 wk (±7)			
		💉	💉		💉		💉				
Informed consent [f]	x				Same as main study OLE schedule		Same as main study OLE schedule		Same as main study OLE schedule	Same as main study OLE schedule	Same as main study OLE schedule
Medical history [g]	x										
Review inclusion/exclusion criteria	x										
Review of re-treatment criteria		x	x								
Physical examination	x	x	x								
Vital signs [h]	x	x	x	x							
12 lead ECG [i]		x									
Weight	x										
Neurological examination	x	x	x	x							
EDSS, and MSFCS	x	x		x							
Adverse events	Only SAEs	x	x	x							
Potential relapses recorded [j]	x	x	x	x							
MFIS, SF-36, EQ-5D (once annually)		x									
Telephone interview [k]		x	x	x							
Concomitant treatment		x	x	x							

Table A8-1 Substudy Schedule of Activities (cont.)

	Unique To Substudy	Substudy Open-Label Treatment Phase (Identical To Main Study OLE) [a, b]							Delayed Dosing Visit [d]	Unscheduled Visit [e]	Withdrawal from Treatment Visit
Cycle		1			2		N [c]				
Visit		D1	D15	w12	D1	w12					
Week in OLE Phase (window in days)	Screening −28 to −1	0 (±5)	2 (±5)	12 (±7)	24 (±5)	36 (±7)	n (±5)	n + 12 wk (±7)			
		💉	💉		💉		💉				
MRI [l] (once per year)	x				Same as main study OLE schedule		Same as main study OLE schedule		Same as main study OLE schedule	Same as main study OLE schedule	Same as main study OLE schedule
Pregnancy test [m]	x	x	x	x							
Antibody titers [n]		x		x							
HAHA [o]		x									
PK samples [p]		x	x	x							
HBV DNA [q]	x	x		(x)							
CD4 count	x			x							
Total Ig, IgA, IgG, IgM	x	x		x							
FACS [r]		x									
Routine safety laboratory tests [s]	x	x		x							
RCR (Protein) [t]		x									
Plasma/ urine banking for JCV [u]		x		x							
Pretreatment with IV methylprednisolone and antihistamine [v]		x	x								

Table A8-1 Substudy Schedule of Activities (cont.)

	Unique To Substudy	Substudy Open-Label Treatment Phase (Identical To Main Study OLE) [a, b]							Delayed Dosing Visit [d]	Unscheduled Visit [e]	Withdrawal from Treatment Visit
Cycle		1			2		N [c]				
Visit		D1	D15	w12	D1	w12					
Week in OLE Phase (window in days)	Screening −28 to −1	0 (±5)	2 (±5)	12 (±7)	24 (±5)	36 (±7)	n (±5)	n + 12 wk (±7)			
		💉	💉		💉		💉				
Administration of IV ocrelizumab [w]		x	x		Same as main study OLE schedule		Same as main study OLE schedule		Same as main study OLE schedule	Same as main study OLE schedule	Same as main study OLE schedule
Open-label clinical genotyping [x]		x		(x)							

β-hCG = β-human chorionic gonadotropin; CD = cluster of differentiation; D = Day; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FACS = fluorescence-activated cell sorting; HAHA = human anti-human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; JCV = John Cunningham virus; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFCS = Multiple Sclerosis Functional Composite Scale; OLE = open-label extension; PCR = polymerase chain reaction; PK = pharmacokinetic; RCR = Roche Clinical Repository; SAE = serious adverse event; SF-36 = Short Form 36; w = week.

[a] **This substudy** can terminate at any moment or cycle (see Section 4.1.9). In case the study is ended, a Withdrawal from Treatment Visit should occur.

[b] All participants entering this substudy will receive a dual ocrelizumab infusion (300 mg IV infusions administered 14 days apart) for the first cycle. For the subsequent cycles, participants will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks.

[c] The assessments requested for N represent the typical schedule of activities during a cycle.

[d] A **delayed dosing visit** will be performed and recorded in the Delayed Dosing Visit eCRF when dosing cannot be administered at the scheduled dosing visit. Other tests/assessments may be done as appropriate.

[e] **Unscheduled visit** (non-dosing): assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant. All participants with new neurological symptoms suggestive of MS worsening or of a relapse should have EDSS performed by the Examining Investigator. Other tests/assessments may be done as appropriate.

[f] **Informed consent** for this substudy will be obtained in written form from all participants at screening in order to meet eligibility for the substudy.

[g] All relevant **medical history** from the time of discontinuation from the main study until screening for the substudy will be reported.

[h] **Vital signs** will be obtained while the participant is in the semi-supine position (after 5 minutes), including pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature. At infusion visits, the vital signs for all participants should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, vital signs should be obtained prior to the study drug or placebo infusion, then every 15 minutes (±5 minutes) for the first hour; then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion. At non-infusion visits, the vital signs may be taken at any time during the visit.

[i] **ECGs (pre- and postdose):** ECGs should be performed within 45 minutes prior to the methylprednisolone infusion in all participants and within 60 minutes after completion of the ocrelizumab infusion. From Week 72 onwards, ECG assessment is not mandatory; it should only be performed if clinically indicated.

[j] Any clinical **relapses** from the time of discontinuation from the main study need to be reported.

[k] A structured **telephone interview** will be conducted by site personnel every 4 weeks to identify and collect information on any changes in the participant's health status that warrant an unscheduled visit (including new or worsening neurological symptoms).

[l] **MRI scans**: a brain MRI scan should be performed at the start of the substudy. Brain MRIs should be done once a year. Brain MRI scans should occur within a window of ±4 weeks of the scheduled visit. Also, brain MRI scans will be obtained in participants withdrawn from the substudy (at a withdrawal visit) if not performed during the previous 4 weeks.

[m] **Urine β-hCG** (sensitivity of at least 25 mIU/mL) will be performed. On infusion visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of childbearing potential. If positive, the participant will not receive the scheduled dose, and for confirmation, a serum pregnancy test will be performed.

[n] **Antibody titers**: measurement of antibody titers against common antigens (mumps, rubella, varicella, and S. pneumoniae) will be performed.

[o] **HAHA**: on infusion visits, samples are collected prior to the methylprednisolone infusion.

[p] **PK samples**: on infusion days in Cycle 1, 2 blood samples should be collected, 1 sample prior to the methylprednisolone infusion, and the second sample 30 minutes (±10 minutes) following the completion of the ocrelizumab infusion. At other times (non-infusion visits), samples may be taken at any time during the visit. For all subsequent cycles after Cycle 1, only 1 PK sample will be taken on Day 1 prior to the methylprednisolone infusion.

[q] **Hepatitis monitoring**: for those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must continue to be repeated every 12 weeks during the substudy.

[r] **FACS**: including CD19 and other circulating B cell subsets, T cells, natural killer cells, and other leukocytes. On infusion days, FACS samples should be collected prior to infusion. See Section 5.13.2 for specific tests.

[s] **Routine safety laboratory tests**: hematology, chemistry, and urinalysis: on infusion visits, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be taken at any time during the visit. Samples collected during unscheduled visits should preferably be sent to and analyzed by the central laboratory and not local unless results are required urgently.

[t] **RCR** (protein) 6-mL blood samples in EDTA tube for plasma will be taken from consenting participants for analysis of protein biomarkers. On infusion visits, samples should be collected 5–30 minutes prior to methylprednisolone infusion.

[u] **Plasma and urine samples for JCV will be collected** at specified timepoints.

[v] All participants will receive **prophylactic treatment** with 100 mg of methylprednisolone IV and an oral or IV antihistamine (such as diphenhydramine 50 mg or equivalent dose of alternative) prior to infusion of ocrelizumab. In the rare cases when methylprednisolone is contraindicated for the participant, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication prior to the infusion. It is also recommended that participants receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab infusions.

[w] **Study drug administration**: the Treating Investigator must review the clinical and laboratory re-treatment criteria prior to re-dosing participants with study drug in all subsequent treatment cycles.

[x] Open-label clinical genotyping: a 3-mL whole blood sample will be taken one time from participants that did not have a sample collected for DNA analysis of HLA-DR and Fc γ polymorphisms during the blinded treatment period. If not collected at the baseline visit (Visit 1), the sample may be collected at any subsequent visit.

SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

All participants must sign and date the most current Institutional Review Board/Ethics Committee's approved written informed consent for this substudy before any study specific assessments or procedures are performed.

A screening examination (medical history and physical examination including vital signs height and weight and neurological examination with EDSS assessment) should be performed within 4 weeks prior to the start of the substudy. Electrocardiogram and laboratory tests (routine safety, pregnancy test in women of childbearing potential and CD4 count) will also be performed. The screening period can be extended to a total period of 8 weeks in cases when a laboratory blood test or MRI scan need to be repeated for confirmation during the screening interval or for other relevant clinical, administrative, or operational reasons. Participants must fulfill all the entry criteria for participation in the study (see Section 5).

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

It should be stated in the medical record that the participant is participating in this clinical study.

PROCEDURES FOR ENROLLMENT OF ELIGIBLE PARTICIPANTS

Once a participant has fulfilled the entry criteria, he or she will be assigned via IxRS a new unique participant identifier to an open-label 300 mg × 2 of ocrelizumab.

Participant eligibility information will be provided to the IxRS by the investigator or the investigator's research staff prior to screening.

The participant identifier numbers are to be allocated sequentially in the order in which the participants are enrolled according to the specification document agreed with the external company/center.

Treatment with the first open-label ocrelizumab infusion should occur within 24 hours of enrollment. In exceptional cases where not all baseline assessments can be completed within 24 hours, the first ocrelizumab infusion can be administered within 48 hours provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing. In particular, there should be no evidence of an ongoing infection at the time of dosing.

No participant may begin treatment prior to enrollment and assignment of a medication number.

OVERVIEW OF SUBSTUDY ASSESSMENTS

With the exception of the mandatory screening period in this substudy, all other substudy periods are identical to those defined for the OLE phase in the main protocol (Section 5.23). The procedures to assess efficacy, safety and laboratory parameters are the same as those described in Section 1.2 of the main protocol.

INVESTIGATIONAL MEDICINAL PRODUCT

During this substudy, all participants will receive open-label ocrelizumab under the same administration schedule and procedures as defined for those participants entering OLE through the main protocol. Details are provided in Section 6 of the main protocol.

SAFETY INSTRUCTIONS AND GUIDANCE

The same provisions apply as in Section 7 of the main protocol.

STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Details of the statistical analyses for this substudy will be provided in the SAP.

Appendix 9 Abbreviations

Abbreviation or Term	Definition
ARR	annualized relapse rate
AUC	area under the concentration–time curve
BCG	Bacille Calmette-Guerin
β-hCG	β human chorionic gonadotropin
CD	cluster of differentiation
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMT	disease-modifying treatment
DSS	Disability Status Scale
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethics committee
EDSS	Expanded Disability Status Scale
FACS	fluorescence-activated cell sorting
FSS	Functional System Score
GGT	gamma glutamyl transferase
HAHA	human anti-human antibody
HBcAb	hepatitis B core antibody
HBsAg	Hepatitis B surface Antigen
HBV	hepatitis B virus
HepCAb	hepatitis C virus antibody
HLA	human leukocyte antigen
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
iDMC	independent Data Monitoring Committee
IFN	interferon
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	Intent-To-Treat
IxRS	interactive voice or Web-based response system
JCV	John Cunningham virus

Abbreviation or Term	Definition
KLH	keyhole limpet hemocyanin
LLN	lower limit of normal
MCS	Mental Component Summary
MFIS	Modified Fatigue Impact Scale
MMRM	mixed-effect model repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFCS	Multiple Sclerosis Functional Composite Scale
NONMEM	nonlinear mixed-effects modeling
OCT	optical coherence tomography
OLE	open-label extension
PASAT	Paced Auditory Serial Addition Test
PCR	polymerase chain reaction
PCS	Physical Component Summary
PD	pharmacodynamic
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PPMS	primary progressive multiple sclerosis
PRO	participant-reported outcome
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RMS	relapsing multiple sclerosis
RCR	Roche Clinical Repository
RNFL	retinal nerve fiber layer
ROW	Rest of World
RPR	rapid plasma reagin
RR	relative reduction
RRMS	relapsing-remitting multiple sclerosis
SAP	Statistical Analysis Plan
SF-36	Short Form-36 Health Survey

Abbreviation or Term	Definition
SPMS	secondary progressive multiple sclerosis
TB	tuberculosis
ULN	upper limit of normal
VEP	visual evoked potential