PROTOCOL

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN COMPARISON WITH INTERFERON-BETA-1A (REBIF®) IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA21092
VERSION NUMBER:	K
TEST COMPOUND:	Ocrelizumab (RO4964913)
STUDY PHASE:	Phase III
EUDRACT NUMBER:	2010-020337-99
IND NUMBER:	100,593
NCT NUMBER:	NCT01247324
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
19-Nov-2021 15:49:52	[redacted]	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
K	See electronic date stamp on title page.
J	27 July 2020
I	18 December 2019
H	3 August 2018
G	4 October 2017
F	4 March 2016
E	4 September 2014
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A	25 August 2010

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PROTOCOL AMENDMENT, VERSION K: RATIONALE

Protocol WA21092 (OPERA I) 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 WA21092 (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 WA21092 to enroll into a new open-label extension study (MN43964) prior to or following the closure of Study WA21092
- 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 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

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN COMPARISON WITH INTERFERON-BETA-1A (REBIF®) IN PATIENTS WITH RELAPSING MULTIPLE SCLEROSIS**
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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 as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Ocrelizumab in Comparison with Interferon-Beta-1a (Rebif®) in Patients with Relapsing Multiple Sclerosis**

Study Rationale

This study is a pivotal Phase III clinical trial, and is composed of the following periods: a double-blind, double-dummy, treatment period, a safety follow-up period, and an open-label extension (OLE) phase. The double-blind, double-dummy, treatment period is designed to demonstrate the efficacy and safety of ocrelizumab in relapsing multiple sclerosis (RMS) in comparison with high-dose, high-frequency (HDHF) interferon (IFN; Rebif). The OLE phase serves to evaluate the long-term safety, tolerability, and efficacy of ocrelizumab treatment in participants with relapsing forms of multiple sclerosis (MS).

This study is part of a broader, confirmatory clinical development program investigating the safety and efficacy of ocrelizumab in participants with both RMS and primary progressive MS (PPMS). An OLE phase of the Phase II Study WA21493/ACT4422G is ongoing for eligible participants with relapsing-remitting MS (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 Objective

The primary objective of this study is to assess whether the efficacy of ocrelizumab 600 mg (given as dual IV infusions of 300 mg on Days 1 and 15 of the first 24-week treatment cycle and as a single infusion of 600 mg on Day 1 of each 24-week treatment cycle thereafter) every 24 weeks is superior to Rebif as measured by the protocol-defined annualized relapse rate (ARR) during nearly 2 years (96 weeks) in participants with RMS.

Secondary Objectives

The key secondary objectives of this study are to evaluate whether the efficacy of ocrelizumab is superior to that of Rebif, as reflected by the following measures:

- The time to onset of confirmed disability progression for at least 12 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period
- The total number of T1 gadolinium (Gd)-enhancing lesions as detected by brain magnetic resonance imaging (MRI) at Weeks 24, 48, and 96
- The total number of new and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96
- The proportion of participants who have confirmed disability improvement for at least 12 weeks with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy, treatment period
- The time to onset of confirmed disability progression for at least 24 weeks, with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period
- The total number of new T1–hypointense lesions (chronic black holes) at Weeks 24, 48, and 96
- The change in Multiple Sclerosis Functional Composite Scale (MSFCS) score from baseline to Week 96
- The percentage change in brain volume as detected by brain MRI from Week 24–96
- The change in Short Form-36 (SF-36) Health Survey Physical Component Summary (PCS) score from baseline to Week 96

- The proportion of participants who have no evidence of disease activity (NEDA) by Week 96

Safety

To evaluate the safety and tolerability of IV ocrelizumab 600 mg (given as dual infusions of 300 mg on Days 1 and 15 of the first 24-week treatment cycle and as a single infusion of 600 mg on Day 1 of each 24-week treatment cycle thereafter) every 24 weeks in participants with RMS (including exploratory endpoints, long-term safety, and tolerability in those participants entering the OLE phase).

Overall Design

Screening

Consenting participants will enter a screening period to be evaluated for eligibility. The screening period will last approximately 2 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. Procedures at screening will include collecting a medical history, medical examination including a thorough neurological exam, Expanded Disability Status Scale (EDSS) testing, ECG, and blood and urine sampling.

Double-Blind, Double-Dummy, Comparative Treatment Period

Eligible participants will be randomized via an interactive voice or Web-based response system (IxRS) into 1 of 2 treatment groups: an ocrelizumab 600 mg regimen (Group A) or an IFN β-1a (Group B) regimen.

During the double-blind, double-dummy, comparative treatment period, participants will be assessed at clinical visits as per the schedule of activities.

Before the next cycle of study drug, participants will be evaluated for pre-specified conditions and laboratory abnormalities to allow for re-treatment.

Participants who discontinue taking study medication within the 96-week, double-blind, double-dummy, comparative phase (treatment period) of the study will enter the safety follow-up period; they will not be eligible for the OLE phase.

Open-Label Extension Phase Screening Period

Participants who complete the 96-week treatment period may become eligible for the OLE phase of the study. Participants will be consented for participation in the OLE phase if they may benefit from treatment with ocrelizumab. Participants who are not willing to participate in the OLE phase of the study will be entered into the safety follow-up period (see below). Participant treatment allocation during the double-blind, double-dummy, treatment period should not be unblinded regardless of participation in the OLE phase.

In the case of a participant who initially declines participation in the OLE phase and subsequently reconsiders the decision, the participant will have up to 24 weeks after the Week 96 visit to enter the OLE phase. In this instance, he or she should not have taken any prohibited medication. Participants who decline participation in the OLE phase should enter the safety follow-up period.

Participants who have consented to participate in the OLE phase will enter an OLE phase screening period to be evaluated for eligibility. The OLE phase screening period will start after all assessments at the Week 96 visit have been performed. This screening period will last up to 4 weeks. The OLE phase screening period could be longer than 4 weeks. If a prolongation of the OLE phase screening period is needed, it should be discussed with the Sponsor on a case-by-case basis.

Information from assessments performed during the Week 96 visit will be utilized to verify the eligibility of the participant for the OLE phase of the study.

During the OLE phase screening period, all participants should receive Rebif/Rebif placebo (depending on initial arm they were assigned to) until the first infusion of Cycle 5.

Participants who withdraw from the OLE phase screening period will be entered into the safety follow-up period.

Open-Label Extension Phase

Duration: the OLE phase will continue as per local regulation or should the Sponsor decide to terminate the ocrelizumab program for MS. Unless terminated earlier for any of the reasons mentioned above, 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 disease-modifying therapy (DMT)* will discontinue from the study completely and will not enter the safety follow-up period.

Treatment: during the OLE phase, all participants will receive the ocrelizumab 600-mg dosing regimen every 24 weeks.

Withdrawal: participants who withdraw from the OLE phase will be entered into the safety follow-up period.

Safety Follow-Up

Participants who discontinue treatment prematurely for any reason during the following periods will be entered into the safety follow-up period:

- Before completion of the 96-week double-blind, double-dummy, treatment period
- During the OLE phase screening period
- During the OLE phase
- Participants who choose not to enter the OLE phase or are not eligible for the OLE phase after completing the 96-week, double-blind, double-dummy, treatment period

In the OLE phase screening period, in the case of a participant who initially declines participation in the OLE phase and subsequently reconsiders the decision, the participant will have up to 24 weeks after the Week 96 visit to enter the OLE phase. In this instance, he or she should not have taken any prohibited medication.

The safety follow-up period will last for 48 weeks starting from the date of the last infusion of ocrelizumab/ocrelizumab placebo. Safety follow-up visits will be performed at 12-week intervals starting from the date of the participant's last visit (the withdrawal from Treatment Visit). *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.*

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

During safety follow-up participants will be assessed at clinical visits every 12 weeks. Telephone interviews will be performed every 4 weeks.

Number of Participants

Approximately 800 participants (400 per treatment arm) will be recruited over a planned recruitment period of 16 months.

Participants will be randomized in 2 groups in a 1:1 ratio. An independent IxRS provider will conduct randomization and hold the treatment assignment code. Participants will be stratified by region (U.S. vs. Rest of World [ROW]) and baseline EDSS (<4 and ≥ 4).

Study Treatment

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

Ocrelizumab is a humanized, glycosylated, monoclonal antibody directed against the cluster of differentiation (CD)20 antigen present on select B cells. Ocrelizumab binds to the CD20 antigen, thereby resulting in B-cell depletion via antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and enhanced apoptosis.

Ocrelizumab was constructed with use of a recombinant DNA technique. This antibody shares an overlapping epitope on CD20 with the chimeric monoclonal antibody, Mabthera®/Rituxan® (rituximab), as determined by direct competition and epitope-mapping experiments. In vitro, ocrelizumab was shown to be approximately 5 times more potent than rituximab in ADCC

activity in a B-cell tumor line over-expressing CD20, approximately 3× less potent via CDC, and approximately equal in inducing apoptosis in a B cell lymphoma cell line.

Substantial proof-of-concept clinical data support the use of B-cell depleting therapies in participants with RMS. Ocrelizumab shares the same basic mechanism of action as rituximab. In a proof-of-concept study, rituximab treatment resulted in a robust reduction in MRI-based measures of CNS inflammation and clinical benefit vs. placebo in participants with RRMS. Study WA21493/ACT4422g, a Phase II study of ocrelizumab in participants with RRMS, provides proof-of-concept support for ocrelizumab efficacy and safety in participants with RRMS.

Ocrelizumab is also known as RO4964913, PRO70769, and rhuMAb 2H7 (refer to the Ocrelizumab Investigator's Brochure [IB] for further information).

Duration of Participation

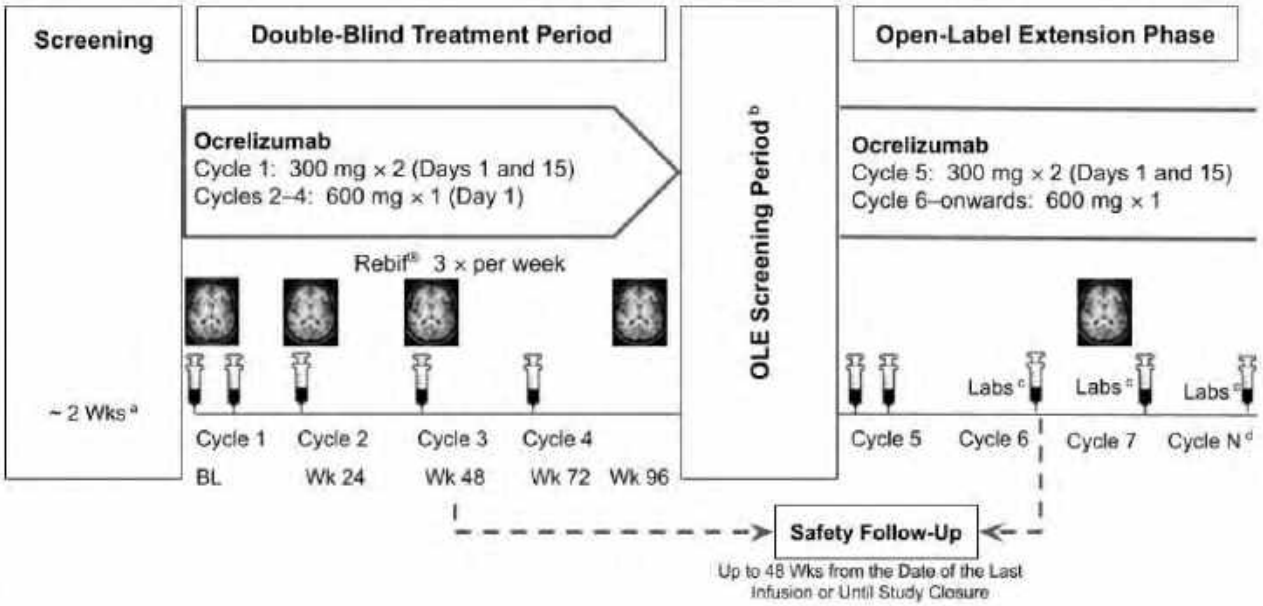
The double-blind, double-dummy treatment duration is 96 weeks followed by an OLE phase.

Independent Data Monitoring Committee

An independent Data Monitoring Committee is not being used.

1.2 STUDY SCHEMA

Figure 1 Overview of the Study Design



BL=baseline; OLE=open-label extension; Wks=weeks.

[a] Screening for the study may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons.

[b] The OLE phase screening period will start after all assessments at the Week 96 visit have been done. It will last up to 4 weeks. For particular reasons, the OLE phase screening period may be longer than 4 weeks. If a prolongation of the OLE phase screening period is needed, it should be discussed with the Sponsor on a case-by-case basis. Note that during the OLE phase screening period, participants should receive Rebif/Rebif placebo until the first infusion of Cycle 5.

[c] To verify that participants meet re-treatment criteria, those in the OLE phase of the study should come to the clinic approximately 2 weeks before the infusions of Cycles 6, 7, etc.

[d] The OLE phase of the study can be terminated at any time. Cycle N represents a typical cycle that occurs every 24 weeks.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period

	Screen	Double-Blind, Double-Dummy Treatment Period												
Cycle		1			2		3		4			Delayed Dosing Visit [a]	Unscheduled Visit [b]	Withdrawal from Treatment Visit
Visit	1	2 BL	3	4	5	6	7	8	9	10	11			
Week	– 2	–	w2	w12	w24	w36	w48	w60	w72	w84	w96			
Study Day (window in days)	– 14	1	15 (± 2)	85 (± 4)	169 (± 2)	253 (± 4)	337 (± 2)	421 (± 4)	505 (± 2)	589 (± 4)	673 (± 2)			
														
Informed consent [c]	x									x [d]				
Medical history	x													
Review of eligibility criteria	x	x									x [d]			
CES-D, MFIS, EQ-5D, SF-36		x					x				x			x
Participant's assessment of treatment benefit							x				x			x
C-SSRS		x		x	x	x	x	x	x	x	x		x	x
Physical examination	x	x	x		x		x		x		x	x		x
Vital signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG (pre- and postdose) [f]	x	x							x					x
Height	x													
Weight	x								x		x			x
Neurological exam and EDSS	x	x		x	x	x	x	x	x	x	x		x	x
MSFCS, LCVA, SDMT		x		x	x	x	x	x	x	x	x		x	x

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period (cont.)

	Screen	Double-Blind, Double-Dummy Treatment Period												
Cycle		1			2		3		4					
Visit	1	2 BL	3	4	5	6	7	8	9	10	11	Delayed Dosing Visit [a]	Unscheduled Visit [b]	Withdrawal from Treatment Visit
Week	– 2	–	w2	w12	w24	w36	w48	w60	w72	w84	w96			
Study Day (window in days)	– 14	1	15 (± 2)	85 (± 4)	169 (± 2)	253 (± 4)	337 (± 2)	421 (± 4)	505 (± 2)	589 (± 4)	673 (± 2)			
														
Karnofsky Performance Status Scale		x			x		x		x		x			x
MRI [g]		x			x		x				x			x
Concomitant Treatment		x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	Only SAEs	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
Telephone interview (every 4 wks) [h]				----------	----------	----------	----------	----------	----------	----------	----------			
Pregnancy test [i]	x	x	x	x	x	x	x	x	x	x	x	x		x
Antibody Titers [j]		x		x	x		x		x		x			x
Protein biomarker sampling [k]		x		x	x		x		x		x			x
HAHA [l]		x			x		x		x		x			x
Plasma/urine banking for JCV [m]		x		x	x	x	x	x	x	x	x			x
PK Samples [n]		x			x		x		x	x	x			x
Thyroid function tests [o]	x				x		x		x		x			x
FSH [p]	x													
Hepatitis Screening [q]	x													

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period (cont.)

	Screen	Double-Blind, Double-Dummy Treatment Period												
Cycle		1			2		3		4			Delayed Dosing Visit [a]	Unscheduled Visit [a]	Withdrawal from Treatment Visit
Visit	1	2 BL	3	4	5	6	7	8	9	10	11			
Week	– 2	–	w2	w12	w24	w36	w48	w60	w72	w84	w96			
Study Day (window in days)	– 14	1	15 (± 2)	85 (± 4)	169 (± 2)	253 (± 4)	337 (± 2)	421 (± 4)	505 (± 2)	589 (± 4)	673 (± 2)			
														
Hepatitis B virus DNA [q]	x	(x)		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)			(x)
RPR	x													
CD4 count	x			x		x		x		x				
IgG				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 [s]	x	x	x	x	x	x	x	x	x	x	x			x
Type I interferon neutralizing antibody assay [t]		x			x		x		x		x			x
Pretreatment with IV methylprednisolone [u]		x	x		x		x		x			x		
Administration of IV. ocrelizumab/ocrelizumab placebo [v]		x	x		x		x		x			x		
Assessment of SC Rebif/Rebif placebo compliance		x	x	x	x	x	x	x	x	x	x		x	x

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period (cont.)

	Screen	Double-Blind, Double-Dummy Treatment Period												
Cycle		1			2		3		4			Delayed Dosing Visit [a]	Unscheduled Visit [b]	Withdrawal from Treatment Visit
Visit	1	2 BL	3	4	5	6	7	8	9	10	11			
Week	– 2	–	w2	w12	w24	w36	w48	w60	w72	w84	w96			
Study Day (window in days)	– 14	1	15 (± 2)	85 (± 4)	169 (± 2)	253 (± 4)	337 (± 2)	421 (± 4)	505 (± 2)	589 (± 4)	673 (± 2)			
														
Administration of SC Rebif/Rebif placebo 3 × /wk		x	x	x	x	x	x	x	x	x	x [y]			

β-hCG = β human chorionic gonadotropin; BL = baseline; CD4 = cluster of differentiation 4; CES-D = Center for Epidemiologic Studies Depression Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; EDTA = ethylenediaminetetraacetic acid; EQ-5D = EuroQoL 5-Dimension; FACS = fluorescence-activated cell sorting; FSH = follicle-stimulating hormone; HAHA = human anti-human antibodies; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepCAb = hepatitis C antibody; JCV = John Cunningham virus; LCVA = Low-Contrast Visual Acuity; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MSFCS = Multiple Sclerosis Functional Composite Scale; OLE = open-label extension; PCR = polymerase chain reaction; PK = pharmacokinetic; RPR = rapid plasma reagin; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test; SF-36 = Short Form-36; sTSH = sensitive thyroid-stimulating hormone; w = week.

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

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

[b] **Unscheduled Visit:** assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant. All participants with new neurological symptoms suggestive of relapse should have EDSS performed by Examining Investigator, whenever possible within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate. Please note: in case of ALT elevations dose modification should be necessary, additional visits may be required for dispensing of study medication.

[c] **Informed Consent** must be obtained in written form from all participants at screening (prior to any study–related procedure) in order to meet eligibility for the study.

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period (cont.)

[d] At the Week 84 Visit, a discussion with the participant regarding participation in the OLE phase should occur if the Treating Investigator is of the opinion that the participant may benefit from treatment with ocrelizumab. An informed consent for the OLE phase should be provided to the participant. It is recommended that the Informed Consent Form of the OLE phase be signed at the Week 96 Visit.

[e] **Vital signs** (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate and temperature) will be obtained while the participant is in the semi-supine position (after 5 minutes). 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 ocrelizumab/ocrelizumab 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] **ECG (pre- and postdose):** on infusion visits ECG should be taken within 45 minutes prior to the methylprednisolone infusion in all participants, and within 60 minutes after completion of the ocrelizumab/ocrelizumab placebo infusion. On non-infusion days, the ECG may be taken at any time during the visit.

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

[h] **A structured telephone interview** will be conducted by site personnel every 4 weeks (±3 days) from Week 8 through the study 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).

[i] **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 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 confirmation, a serum pregnancy test, will be performed.

[j] **Antibody Titers**: measurement of antibody titers against common antigens (mumps, rubella, varicella and Streptococcus pneumoniae) will be performed.

[k] **Protein biomarker sampling:** 1 serum sample (6 mL) will be collected from all participants for analysis of protein biomarkers. On infusion visits, samples should be collected 5–30 minutes prior to methylprednisolone infusion.

[l] **HAHA**: On infusion visits, serum samples are collected 5–30 minutes prior to the methylprednisolone infusion.

[m] **Plasma and urine samples for JCV will be collected** at specified timepoints and analyzed in batches, if decided by the Sponsor.

[n] **PK samples:** on the infusion day at Week 72, two serum samples should be collected, one sample collected 5–30 minutes prior to the methylprednisolone infusion and the second sample 30 minutes (± 10 minutes) following the completion of the ocrelizumab/ocrelizumab placebo infusion. For all other infusion visits, a blood sample should be collected 5–30 minutes before the methylprednisolone infusion. At other times (non-infusion visits) samples may be collected at any time during the visit.

[o] **sTSH** will be tested at screening and during the double-blind, double-dummy treatment period. Thyroid autoantibodies will be assayed only at screening.

[p] **FSH**: only applicable to women to confirm the postmenopausal status.

Table 1 Schedule of Activities: Screening through the End of the Double-Blind, Double-Dummy Treatment Period (cont.)

[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 during the treatment period.

[r] **FACS**: including CD19 and other circulating B-cell subsets, T cells, natural killer cells, and other leukocytes. On infusion visits, blood samples should be collected prior to the infusion of methylprednisolone.

[s] **Routine safety laboratory:** 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 collected at any time during the visit.

[t] **Type I interferon neutralizing antibody assay:** at baseline (Visit 2), sample should be collected before first Rebif/Rebif placebo injection. At subsequent visits, samples should be collected at least 36 hours following last injection of Rebif/Rebif placebo.

[u] All participants receive **prophylactic treatment** with 100 mg of methylprednisolone IV prior to infusion of ocrelizumab /ocrelizumab placebo. In the rare case when the use of methylprednisolone is contraindicated for the participant, use of an equivalent dose of an alternative steroid 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) and an IV or oral antihistaminic, such as diphenhydramine 50 mg, 30–60 minutes prior to ocrelizumab/ocrelizumab placebo.

[v] **Administration (infusion) of IV ocrelizumab/ocrelizumab placebo**: the Treating Investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab/ocrelizumab placebo.

[w] If the participant enters OLE phase screening period, Rebif / Rebif placebo should be provided to the participant at the Week 96 visit (please see Section 5.17.1).

Table 2 Schedule of Activities: Safety Follow-Up

	Safety Follow-Up	End of Observation or Withdrawal from Safety Follow-Up
Assessments	**Visits every 12 weeks (± 7 days) [a]**	
Urine pregnancy test	x	x
Routine Safety Labs [b]	x	x
FACS [c]	x	x
Total Ig, IgA, IgG, IgM	x [d]	x
HAHA (optional) [e]	x	
Ocrelizumab concentration sample (optional) [e]	x	
Antibody titers	x [d]	x
Hepatitis B viral DNA [f]	(x)	(x)
Protein biomarker sampling [g]	x [d]	x
Vital Signs	x	x
EDSS	x	x
Neurological examination	x	x
Physical examination	x [d]	x
Potential relapses recorded	x	x
Adverse events	x	x
Concomitant Medication	x	x
MRI [h]	(x)	
Telephone interview [i]	x	

Table 2 Schedule of Activities: Safety Follow-Up (cont.)

CD=cluster of differentiation; EDSS=Expanded Disability Status Scale; EDTA=ethylenediaminetetraacetic acid; FACS=fluorescence-activated cell sorting; HAHA=human anti-human antibodies; HBcAb=hepatitis C antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; MRI=magnetic resonance imaging.

[a] Safety follow-up will be carried out for 48 weeks starting from the date of last infusion of ocrelizumab. Visits will be performed at 12-week intervals starting from the date of the participant's Withdrawal from Treatment Visit. *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. The last scheduled safety follow-up visit will become the End of Observation visit and the participant will have completed the study. *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] **Routine safety laboratory examination**: hematology, chemistry and urinalysis.

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

[d] Needs to be assessed only every 24 weeks.

[e] **HAHA and ocrelizumab drug concentration samples**: in 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.

[f] **Hepatitis monitoring**: hepatitis to be monitored only in participants with screening results of HBsAg-negative, HBcAb-positive and HBV DNA negative, inclusive.

[g] **Protein biomarker sampling**: 6 mL blood sample in a plain tube without EDTA for serum isolation will be collected from all participants for analysis of protein biomarkers.

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

[i] A structured **telephone interview** will be performed by site personnel every 4 weeks (±3 days) between visits until 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).

Table 3 Schedule of Activities: Open-Label Extension Phase

	OLE Screen	Open-Label Extension Phase [a]											Delayed dosing Visit [c]	Unscheduled Visit [d]	Withdrawal from Treatment Visit
Cycle [a]		5			6 [a]		7 [a]		8 [a]		N [a, b]				
Visit		12	13	14	15	16	17	18	19	20					
Week in OLE phase (window in days)		0[2]	2 (±2)	12 (±7)	22 (±7)	24 (±5)	46 (±7)	48 (±5)	70 (±7)	72 (±5)	n-2 wk (±7)	n (±5)			
		💉	💉			💉		💉		💉		💉			
Informed consent [e]	x														
Review of eligibility criteria	x	x													
Review of re-treatment criteria		x	x			x		x		x		x	x		
Administration of SC Rebif / Rebif placebo 3 x/wk [f]	x														
Assessment of SC Rebif/ Rebif placebo compliance		x													
Pretreatment with IV methylprednisolone and antihistamine [g]		x	x			x		x		x		x	x		
Administration of IV ocrelizumab [h]		x	x			x		x		x		x	x		
Physical examination		x	x			x		x		x		x	x		x
Vital signs, weight [i]		x	x	x		x		x		x		x	x	x	x
12-lead ECG (pre- and postdose, once yearly) [j]		x	x							(x)		(x)			(x)
Neurological exam and EDSS		x		x		x		x		x		x		x	x
Routine safety laboratory tests [k]		x		x	x		x		x		x			x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 3 Schedule of Activities: Open-Label Extension Phase (Cont.)

	OLE Screen	Open-Label Extension Phase [a]											Delayed dosing Visit [c]	Unscheduled Visit [d]	Withdrawal from Treatment Visit
Cycle [a]		5			6 [a]		7 [a]		8 [a]		N [a, b]				
Visit		12	13	14	15	16	17	18	19	20					
Week in OLE phase (window in days)		0[2]	2 (±2)	12 (±7)	22 (±7)	24 (±5)	46 (±7)	48 (±5)	70 (±7)	72 (±5)	n-2 wk (±7)	n (±5)			
Concomitant treatments		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
Pregnancy test [l]		x	x	x		x		x		x		x	x		x
Antibody titers [m]		x		x	x		x		x		x				x
Total Ig, IgA, IgG, IgM		x			x		x		x		x				
CD4 count		x	x		x		x		x		x				
HAHA (optional) [n]		x													
Ocrelizumab concentration sample (optional) [n]		x													
Telephone interview (every 4 weeks) [o]				→											
EQ-5D		x					x								
SF-36 (once yearly) [p]							x				(x)				
Protein biomarker sampling [q]		x		x	x		x		x		x				
FACS [r]			x	x	x		x		x		x				
Hepatitis B virus DNA [s]				(x)	(x)		(x)		(x)		(x)				
MRI (once yearly) [t]							x				(x)				x
Participant's Assessment of Treatment Benefit (once yearly)							x				(x)				

Table 3 Schedule of Activities: Open-Label Extension Phase (Cont.)

	OLE Screen	Open-Label Extension Phase [a]											Delayed dosing Visit [c]	Unscheduled Visit [d]	Withdrawal from Treatment Visit
Cycle [a]		5			6 [a]		7 [a]		8 [a]		N [a, b]				
Visit		12	13	14	15	16	17	18	19	20					
Week in OLE phase (window in days)		0[2]	2 (±2)	12 (±7)	22 (±7)	24 (±5)	46 (±7)	48 (±5)	70 (±7)	72 (±5)	n-2 wk (±7)	n (±5)			
		↓	↓			↓		↓		↓		↓			
SDMT (once yearly) [u]		x						x				(x)			
Optional samples for RBR (CSF and blood) [v]	x														

β-HCG = β human chorionic gonadotropin; CD4 = cluster of differentiation 4; CSF = cerebrospinal fluid; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQoL 5-Dimension; FACS = fluorescence-activated cell sorting; HAHA = human anti-human antibodies; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MRI = magnetic resonance imaging; OLE = open-label extension; PCR = polymerase chain reaction; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SF-36 = Short Form-36; wk = week.

[a] **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.* **The OLE phase** starts at the first infusion of Cycle 5. The OLE phase screening period will start after all assessments at the Week 96 visit have been performed, and it should last approximately 4 weeks. It is possible that the OLE phase screening period could be longer than 4 weeks. If a prolongation of the OLE phase screening period is needed, it should be discussed with the Sponsor on a case-by-case basis.

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

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

[d] **Unscheduled Visit**: assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant. All participants with new neurological symptoms suggestive of relapse should have EDSS performed, whenever possible within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.

[e] The **informed consent** should have been provided to the participant at the Week 84 Visit and signed by the participant at the Week 96 visit.

Table 3 Schedule of Activities: Open-Label Extension Phase (Cont.)

[f] During the OLE phase screening period, SC administration Rebif / Rebif placebo 3 times per week should occur until one day prior to the first infusion of ocrelizumab of Cycle 5 (beginning of OLE phase). If during this period, the participant decides not to participate in the OLE phase, then administration of Rebif/Rebif placebo 3 times per week should stop immediately, and the participant will be entered in the safety follow-up period.

[g] All participants receive prophylactic treatment with 100 mg of methylprednisolone IV and an oral or IV antihistamine (such as diphenhydramine 50 mg or an equivalent dose of an alternative) prior to infusion of 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 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).

[h] **Administration (infusion) of IV ocrelizumab**: the investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The participant will need to remain under observation at the clinical for at least 1 hour after infusion. It is anticipated that the participant will need to stay at the hospital or clinical site for a full day for the infusion visit.

[i] **Vital signs** (i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature) will be obtained while the participant is in the semi-supine position (after 5 minutes). Vital signs should be collected within 45 minutes prior to the methylprednisolone infusion in all participants. In addition, vital signs should be obtained prior to ocrelizumab 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. Weight measurement is to be performed at OLE Visit 0 (Cycle 1) and OLE Withdrawal from Treatment Visit only.

[j] **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 Visit 20 onwards, ECG assessment is not mandatory; it should only be performed if clinically indicated.

[k] **Routine safety laboratory tests:** hematology, chemistry, and urinalysis. On infusion visits at Cycle 5, all urine and blood samples should be collected prior to the infusion of methylprednisolone. At other times, samples may be collected at any time during the visit.

[l] **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.

[m] **Antibody Titers**: measurement of antibody titers against common antigens (mumps, rubella, varicella, and *Streptococcus pneumoniae*) will be performed.

[n] **HAHA and ocrelizumab drug concentration 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.

[o] A structured **telephone interview** will be conducted by site personnel every 4 weeks (±3 days) from Cycle 5 (Week 8 of OLE phase) through the study 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).

Table 3 Schedule of Activities: Open-Label Extension Phase (Cont.)

[p] **SF-36, The Short Form Health Survey**, is to be performed once yearly during the OLE phase.

[q] **Protein biomarker sampling:** 1 serum sample (6 mL) will be collected from all participants for analysis of protein biomarkers. On infusion visits, samples should be collected 5–30 minutes prior to methylprednisolone infusion.

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

[s] **Hepatitis monitoring**: for those participants enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks during the treatment period.

[t] **MRI**: 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 last 4 weeks.

[u] **SDMT, Single Digit Modalities Test**, is to be performed once yearly during the OLE phase.

[v] **Optional samples for RBR (CSF and blood):** one-time optional CSF sample, paired plasma samples, and blood samples for the RBR collected at any timepoint during 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. Multiple sclerosis affects approximately 2.5 million people worldwide: it is one of the most common neurological disorders and causes of disability of young adults, especially in Europe and North America (World Health Organization 2010). 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 examination of cerebrospinal fluid (CSF; McDonald et al. 2001; Polman et al. 2011).

Multiple sclerosis is clinically subcategorized into 4 phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression (Lublin and Reingold 1996). These include relapsing-remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS; and secondary progressive MS (SPMS).

Approximately 80% of patients with MS present with RRMS. If left untreated, most patients with RRMS will transition into SPMS (with progressive loss of neurologic function in the absence of relapses) within 20 years. The term relapsing MS (RMS) applies to those patients with either RRMS or SPMS who continue to suffer relapses. Patients with RMS, whether or not they suffer from neurologic progression in the absence of relapses, have a common, inflammatory pathophysiology and, therefore, constitute a common target for treatment.

Currently available first-line therapies for the treatment of either RMS or RRMS include Rebif® and Avonex® (interferon [IFN])–β-1a, Betaferon®/Extavia® (IFN–β-1b) and Copaxone® (glatiramer acetate). The currently approved first-line treatments are only modestly effective in reducing the frequency of relapses and preventing disability in patients with RMS. The magnitude of these disease-modifying effects are an approximately 30% relative improvement versus placebo (Filippini et al. 2003). The first-line disease-modifying agents reduce the frequency of new episodes but do not reverse fixed deficits and have variable effects on long-term disability progression (Compston and Coles 2008).

Gilenya® (fingolimod; FTY720) is an oral modulator of sphingosine-1 phosphate (S1P) receptors, a ubiquitous group of transmembrane receptors involved with cellular growth

and differentiation. Fingolimod's immunomodulatory effects are believed to be due to binding to and internalization of the S1P receptor on lymphocytes, thereby rendering them insensitive to S1P gradients in lymph and inhibiting egress from lymph nodes and other secondary lymphoid organs. Fingolimod is known to readily cross the blood-brain barrier, and S1P receptors are present on glial cells and neurons. However, the implications of any possible direct CNS S1P receptor modulation effects are currently unknown. Fingolimod was shown to reduce the annualized relapse rate (ARR) by approximately 50% versus both placebo and intramuscular (IM) IFN β-1a 30 mcg weekly in confirmatory Phase III clinical trials. Because of the presence of S1P receptors on many different cell types, the adverse event profile of fingolimod is complex and may include effects on cardiac, ophthalmic, hepatic, and pulmonary function, as well as an increased risk of infection due to inhibition of lymphocyte trafficking. Fingolimod was approved in 2010 by the U.S. Food and Drug Administration (FDA) for patients with relapsing forms of MS and by the European Medicines Agency in 2011 for use in patients who have previously failed first-line disease-modifying therapy (DMT) or who have highly active disease.

Tysabri® (natalizumab) is a monoclonal antibody directed against α-4 β-1 integrin (VLA-4), an adhesion molecule expressed on activated lymphocytes. Natalizumab binds to VLA-4, inhibiting trafficking of activated lymphocytes into the CNS and other extravascular tissues. Natalizumab was shown to produce a 66% relative reduction in ARR versus placebo in a Phase III clinical trial. Natalizumab use is generally limited to patients with RRMS who have failed to respond to first-line DMT or to patients with highly active RRMS due to a risk of progressive multifocal leukoencephalopathy (PML).

Aubagio® (teriflunomide) is a once-daily, oral immunomodulator that inhibits dihydroorotate dehydrogenase, a key mitochondrial enzyme involved in de novo pyrimidine synthesis for DNA replication, and reduces T-cell and B-cell proliferation and function in response to autoantigens. Teriflunomide was approved by the FDA in 2012 for the treatment of relapsing forms of MS. Two Phase III trials showed a significant reduction in ARR of teriflunomide against placebo (O'Connor et al. 2011; Kappos et al. 2012). A third Phase III trial, TENERE, showed that teriflunomide was not statistically different than IFN β-1a in terms of risk of treatment failure (NCT00883337). Risk of treatment failure was defined as the occurrence of a confirmed relapse or permanent treatment discontinuation for any cause, whichever came first.

Novantrone® (mitoxantrone), a chemotherapeutic agent, is also approved for the treatment of relapsing MS in the United States but is generally reserved for secondary progressive and severe relapsing-remitting forms of disease. Other drugs have been used with varying degrees of success, including corticosteroids, methotrexate (MTX), cyclophosphamide, azathioprine, and IV immunoglobulin.

Despite significant advances in MS therapy, many patients continue to experience disease activity; thus, a need to develop more effective and better tolerated therapies for the treatment of RMS remains.

2.1.2 Ocrelizumab

Ocrelizumab is a humanized, glycosylated, monoclonal antibody directed against the cluster of differentiation (CD)20 antigen present on select B cells. Ocrelizumab binds to the CD20 antigen, thereby resulting in B-cell depletion via antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and enhanced apoptosis.

Ocrelizumab was constructed with use of a recombinant DNA technique. This antibody shares an overlapping epitope on CD20 with the chimeric monoclonal antibody, Mabthera®/Rituxan® (rituximab), as determined by direct competition and epitope-mapping experiments. In vitro, ocrelizumab was shown to be approximately 5 times more potent than rituximab in ADCC activity in a B-cell tumor line over-expressing CD20, approximately 3× less potent via CDC, and approximately equal in inducing apoptosis in a B cell lymphoma cell line.

Substantial proof-of-concept clinical data support the use of B-cell depleting therapies in participants with RMS. Ocrelizumab shares the same basic mechanism of action as rituximab. In a proof-of-concept study, rituximab treatment resulted in a robust reduction in MRI-based measures of CNS inflammation and clinical benefit vs. placebo in participants with RRMS (Hauser et al. 2008). Study WA21493/ACT4422g, a Phase II study of ocrelizumab in participants with RRMS, provides proof-of-concept support for ocrelizumab efficacy and safety in participants with RRMS; please see Section 2.1.4.1 for more details.

Ocrelizumab is also known as RO4964913, PRO70769, and rhuMAb 2H7 (refer to the Ocrelizumab Investigator's Brochure [IB] for further information).

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 (OCBs) and increased intrathecal IgG synthesis in diagnostic criteria for MS (Sidén 1979; McDonald et al. 2001; Polman et al 2011). 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 fundamentally 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 participants with MS. Molecular analysis of both lesional and CSF B-cell repertoires reveals dominant, clonally-expanded B cell populations exhibiting somatic hypermutation in the antigen-recognizing third complementarity

determining regions (CDR3) of Ig heavy chains, predominately within the variable heavy 4 *(VH4)* gene family (Owens 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 peripheral blood of participants 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, complementary DNA (cDNA) transcriptomes of clonally-expanded, affinity-matured B cells isolated from the CSF of participants with MS have been sequence-matched to specific IgG OCBs 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).

Both antibody-dependent and independent hypotheses for the role of B cells in MS pathophysiology have been postulated and are currently the subject of intensive research. B cells may differentiate into plasma cells and produce CNS-directed auto-antibodies, potentially triggering cellular- and CDC. Although a pathogenic role of anti-myelin antibodies in MS has not been established, they have been detected in the CSF of participants 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 because 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 (Qin et al. 1998; Serafini et al. 2004; 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 auto-antigenic B cell activation, maturation, and clonal expansion (Aloisi and Pujol-Borrell 2006). Patients with SPMS who exhibit these lymphoid structures have been found to have worse progression rates 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. 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. 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, which makes it a potentially attractive pharmacological agent to test for therapeutic potential in patients with MS.

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 gadolinium (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 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 versus 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 to 111.5) and 3.39/100 PY (95% CI: 1.27 to 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 to 126.84) and 5.31/100 PY (95% CI: 1.71 to 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.

2.1.4.2 Long-Term Results of Phase II Study WA21493/ACT4422G

To further understand the long-term effect of ocrelizumab therapy, the Phase II Study WA21493/ACT4422G was designed with a 48-week treatment-free period after the 96-week treatment period with ocrelizumab. Across all treatment groups, 86%–91% of the 220 initially randomized participants entered the treatment-free period. This included participants who had withdrawn from treatment. Subsequently, 73%–82% of participants completed Week 120; 69%–80% completed Week 144; and 36%–56% of participants entered a 24-week, drug-free observation period after B-cell repletion at Week 144. During the treatment-free period, ARR remained at low levels similar to those during the treatment period (0.04–0.29 across treatment groups), with no indication of increase or rebound. The mean number of Gd-enhancing T1 lesions remained at 0 at Week 144 in the ocrelizumab 600 mg group and increased from 0 at Week 96 to 0.3 at Week 144 in the ocrelizumab 1000 mg group. Furthermore, no imbalance was found in the rates of adverse events or serious adverse events across all treatment groups over 144 weeks. No new serious infections and no opportunistic infections were reported since the last ocrelizumab administration. Infection rates did not increase over time; at Week 144, infection rates were 6.5% and 11.1% with the ocrelizumab 600 mg and 1000 mg regimens, respectively. The most common types of infections were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (Kappos et al. 2012).

The long-term efficacy data from the Phase II Study WA21493/ACT4422G show that the low-level of disease activity observed after ocrelizumab treatment was sustained through Week 144. This includes the observation that no Gd-enhancing T1 lesions were observed in the ocrelizumab 600 mg group at Week 144, which indicates a long-term anti-inflammatory effect of ocrelizumab on the CNS. Up to Week 144, no new safety issues were observed with ocrelizumab. In particular, no increases in infections and no new serious adverse events occurred, which indicates a positive benefit/risk profile. Currently, eligible participants continue to receive ocrelizumab treatment in the open-label extension (OLE) phase of this study.

2.1.4.3 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).

2.1.4.4 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 versus 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 due to 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).

2.1.5 Rebif

The active comparator for this study is Rebif (IFN β-1a), which has been approved for treatment of RMS.

The efficacy and safety of Rebif was demonstrated in the PRISMS study (The Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis), which led to the approval of Rebif in RMS. This was a multicenter controlled trial of 560 participants with an EDSS score between 1.0 and 5.0 and at least 2 relapses in the preceding 2 years. Participants were randomized to 2-year treatment with placebo or IFN β-1a (22 or 44 μg SC 3× weekly). Following the 2 years of treatment, compared with placebo, both doses of Rebif showed significant beneficial effects on major efficacy outcome measures. A non-significant trend towards greater efficacy with the higher dose was noted for most clinical measures, as was a statistically significant dose effect favoring the higher dose in terms of impact on the number of T2-active lesions. In a subgroup of participants with more severe disease (baseline EDSS >3.5), the 44-μg dose delayed progression of disability significantly better than either the placebo or the

22 μg dose. Neutralizing antibodies were significantly less frequent in the 44 μg group than in the low-dose group (PRISMS Study Group 1998).

After 2 years, participants who had initially received placebo in the PRISMS study were re-randomized to receive Rebif (22 or 44 μg SC 3× weekly) and were followed up for an additional 2 years. By the end of the 4-year period, participants who had switched from placebo to Rebif experienced an approximate 50% reduction in ARR compared with the ARR at the end of Year 2. Moreover, after 4 years, the higher dose approached significance for ARR (0.8 for 22 μg vs. 0.72 for 44 μg; p=0.069). The mean ARR was significantly lower in participants who had received Rebif for the full 4 years compared with those who had received placebo for the first 2 years. During Years 3 and 4, relapse rates were significantly lower for the 44-μg group, and relapse rates decreased . Progressively, each year of treatment had 0.92, 0.82, 0.57, and 0.44 relapses/year. Participants who received the highest cumulative dose of active therapy had the lowest rates of disability progression. The time to first confirmed EDSS progression was 42.1 months for the 44-μg group compared with 24.2 months for the crossover group. The time to first confirmed progression did not differ significantly between the 22-μg group (35.9 months) and the crossover group (PRISMS Study Group 2001).

Rebif showed superiority vs. Avonex in the EVIDENCE trial. This was a randomized, controlled, multicenter trial that compared the efficacy and safety of Rebif 44 μg SC 3×weekly and Avonex 30 μg IM once weekly in 677 participants with RRMS. The primary endpoint was the proportion of participants who were relapse-free at 24 weeks, and the principal MRI endpoint was the number of active lesions per participant per scan at 24 weeks. After 24 weeks, 74.9% of participants receiving Rebif 44 μg 3× a week remained relapse free compared with 63.3% of those given Avonex 30 μg IM once a week. Participants receiving Rebif 44 μg 3× a week had fewer active MRI lesions (p=0.001 at 24 and 48 weeks) compared with those receiving Avonex 30 μg IM once a week. Injection site reactions were more frequent with Rebif 44 μg 3× a week (83% vs. 28%, p=0.001), and asymptomatic abnormalities of liver enzymes (18% vs. 9%, p=0.002) and altered leukocyte counts (11% vs. 5%, p=0.003) were noted, unlike with the Avonex 30 μg IM once a week dose. Neutralizing antibodies developed in 25% of Rebif 44 μg 3× a week participants and in 2% of participants receiving IFN β-1a 30 μg once a week (Panitch et al. 2002).

Rebif has also been studied in the SPMS population. The SPECTRIMS study was a multicenter, randomized, parallel-group, placebo-controlled study which tested 2 doses of Rebif in participants with SPMS. Participants had to have clinically definite SPMS, which was defined as progressive deterioration of disability for at least 6 months with an increase of at least 1 EDSS point over the previous 2 years (or 0.5-point between EDSS scores of 6.0 and 6.5), with or without relapses, following an initial course of RRMS. Baseline EDSS scores had to be from 3.0–6.5 and the pyramidal functional score at least 2. Participants were randomized to 3-year treatment with placebo or IFN β-1a (22 or 44 μg SC 3× weekly). The primary outcome was time of confirmed progression,

defined as an increase from baseline of at least 1 EDSS point (or 0.5-point if baseline EDSS ≥ 5.5), confirmed 3 months later with no intervening score lower than the minimum required level. The primary outcome was not significantly influenced by treatment with Rebif compared with placebo (p=0.146). A significant benefit was seen on relapse rate for both doses of Rebif. These findings suggest that treatment with Rebif has clinical benefit in SPMS, predominantly by affecting relapses, but only a modest effect on disability (SPECTRIMS Study Group 2001).

In controlled clinical trials, the most commonly observed adverse reactions were: injection site reactions, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, and myalgia), elevated liver enzymes, hematological abnormalities, abdominal pain, and depression. Most of these adverse reactions are unique to treatment with IFN β-1a and thereby present potential difficulties in maintaining blinding in controlled clinical trials. Summary of the most frequent Rebif adverse reactions by MedDRA System Organ Class have been summarized in Table 4.

Table 4 Summary of the Most Frequent Rebif Adverse Reactions by MedDRA System Organ Class

System Organ Class	Very Common ADR Frequency of Occurrence ≥ 1/10	Common ADR Frequency of Occurrence ≥ 1/100 to 1/10
General disorders and administration site conditions	Injection site inflammation, injection site reaction, influenza-like symptoms	Injection site pain, fatigue, rigors, fever
Investigations	Asymptomatic transaminase increase	Severe elevation of transaminase
Blood and lymphatic system disorders	Neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia	
Psychiatric disorders		Depression, insomnia
Nervous system disorders	Headache	
Gastrointestinal disorders		Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders		Pruritus, rash, erythematous rash, macula-papular rash
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia

Source: Rebif Summary of Product Characteristics 2010. Please refer to local label for more details.

ADR=adverse drug reaction.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in participants taking Rebif. Treatment with Rebif should be stopped immediately if jaundice or other symptoms of liver dysfunction appear

(Rebif E.U. Summary of Product Characteristics; Rebif U.S. Package Insert [USPI]). Please see Section 6.2.2 for further details.

Neutralizing antibodies to IFN β-1a can develop in some participants, usually following the first year of therapy. Long-term consequences of these antibodies are still not known; however, current evidence shows that they may reduce the efficacy of the drug. The antibodies tend to cross-react with different IFN β formulations. For this reason, switching to another IFN β drug is unlikely to be effective (Lim and Constantinescu 2010; Polman et al. 2010).

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

This study is a pivotal Phase III clinical trial, and is composed of the following periods: a double-blind, double-dummy, treatment period, a safety follow-up period, and an OLE phase. The double-blind, double-dummy, treatment period is designed to demonstrate the efficacy and safety of ocrelizumab in RMS in comparison with high-dose, high-frequency (HDHF) IFN (Rebif). The OLE phase serves to evaluate the long-term safety, tolerability, and efficacy of ocrelizumab treatment in participants with relapsing forms of MS.

This study is part of a broader, confirmatory clinical development program investigating the safety and efficacy of ocrelizumab in participants with both 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 4.1.6 for further details on study design and choice of comparator.

A benefit–risk assessment was conducted to determine whether there is any impact on the concomitant use of severe acute respiratory syndrome coronavirus 2 (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).

3. OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess whether the efficacy of ocrelizumab 600 mg (given as dual IV infusions of 300 mg on Days 1 and 15 of the first 24-week treatment cycle and as a single infusion of 600 mg on Day 1 of each 24-week treatment cycle thereafter) every 24 weeks is superior to Rebif as measured by the protocol-defined ARR (see Section 5.10.2.1 for the definition of protocol-defined relapse) during nearly 2 years (96 weeks) in participants with RMS.

3.2 SECONDARY OBJECTIVES

The key secondary objectives of this study are to evaluate whether the efficacy of ocrelizumab is superior to that of Rebif, as reflected by the following measures:

- The time to onset of confirmed disability progression for at least 12 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period (see Section 5.10.2.2 for the definition of confirmed disability progression)
- The total number of T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96
- The total number of new and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96
- The proportion of participants who have confirmed disability improvement for at least 12 weeks with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy, treatment period
- The time to onset of confirmed disability progression for at least 24 weeks, with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period (see Section 5.10.2.2 for the definition of confirmed disability progression)
- The total number of new T1–hypointense lesions (chronic black holes) at Weeks 24, 48, and 96

- The change in Multiple Sclerosis Functional Composite Scale (MSFCS) score from baseline to Week 96
- The percentage change in brain volume as detected by brain MRI from Week 24–96
- The change in Short Form-36 (SF-36) Health Survey Physical Component Summary (PCS) score from baseline to Week 96
- The proportion of participants who have no evidence of disease activity (NEDA) by Week 96

3.2.1 Safety

To evaluate the safety and tolerability of IV ocrelizumab 600 mg (given as dual infusions of 300 mg on Days 1 and 15 of the first 24-week treatment cycle and as a single infusion of 600 mg on Day 1 of each 24-week treatment cycle thereafter) every 24 weeks in participants with RMS (including exploratory endpoints, long-term safety, and tolerability in those participants entering the OLE phase).

3.2.2 Pharmacokinetics/Pharmacodynamics

To explore the pharmacokinetics, immunogenicity, and pharmacodynamics of ocrelizumab in participants with RMS.

3.3 EXPLORATORY OBJECTIVES

- The change in low-contrast visual acuity from baseline to Weeks 48 and 96
- The change in the Symbol Digit Modalities Test (SDMT) from baseline to Weeks 48 and 96
- The proportion of relapse-free participants by Week 96
- The change in total T2 hyperintense lesion volume as detected by brain MRI from baseline to Week 96
- The ARR, based on all clinical relapses at the end of the 96-week comparative treatment period (protocol-defined relapses are a subset of all clinical relapses)
- The ARR of relapses requiring IV steroid therapy
- The ARR of severe relapses
- The percentage change in brain volume as detected by brain MRI from baseline to Week 96
- The change in MSFCS score from baseline to Week 48
- The cumulative change in EDSS scores measured in area under the concentration–time curve (AUC) by Week 96
- The change in EDSS from baseline to Week 96
- The change in Timed 25-Foot Walk Test (T25FWT) from baseline to Week 96
- The change in 9-Hole Peg Test (9-HPT) from baseline to Week 96
- The change in paced auditory serial addition test (PASAT) from baseline to Weeks 48 and 96

- The time to onset of a sustained 20% increase in 9-HPT for at least 12 weeks
- The time to onset of a sustained 20% increase in T25FWT for at least 12 weeks
- The change in fatigue, as measured by the Modified Fatigue Impact Scale (MFIS) total score from baseline to Week 96
- The change in participant-reported depressive symptoms, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D), from baseline to Week 96
- Analyses of EQ-5D, collected at baseline, Week 48, and Week 96
- The change in Karnofsky Performance Status Scale score from baseline to Week 96
- The percentage change in cortical grey-matter volume from baseline to Week 96
- The percentage change in white matter volume from baseline to Week 96
- The proportion of participants who have confirmed disability improvement sustained for at least 24 weeks, with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy, treatment period
- The proportion of participants who have disability improvement sustained for at least 12 weeks and sustained until the end of the 96-week, double-blind, double-dummy treatment period, with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy, treatment period
- The duration of the confirmed disability improvement
- The proportion of participants who, at Week 96, have improved, stable, or worsened disability, compared with baseline
- The change in Quality of Life, as measured by the SF-36 version 2 Mental Component Summary (MCS) score from baseline to Week 96
- The long-term effects of ocrelizumab on clinical and MRI parameters of disease activity and progression during the OLE phase of the study
- The long-term safety of ocrelizumab treatment during the OLE phase of the study
- The effects of switching from Rebif to ocrelizumab treatment

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 5.12 for details on the RBR.

3.5 OPTIONAL EXPLORATORY SUBSTUDIES

Consenting participants who enrolled in the main Study WA21092 and who are eligible will be offered the opportunity to participate in optional substudies. See Section 5.16 for details.

3.5.1 Optical Coherence Tomography Exploratory Substudy

This substudy 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 5.16.1 and Appendix 8). In July 2017, Roche determined that sufficient data had been collected from the optical coherence tomography (OCT) substudy. During 2017 and 2018, participants will discontinue participation in the OCT substudy but may continue in the OLE phase.

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN AND DOSING REGIMEN

A schematic of the study design is presented in Figure 1. The study will consist of the following periods.

4.1.1 Screening

Consenting participants will enter a screening period to be evaluated for eligibility. The screening period will last approximately 2 weeks, but it may be prolonged for up to 8 weeks for relevant clinical, administrative, or operational reasons. Procedures at screening will include collecting a medical history, medical examination including a thorough neurological exam, EDSS testing, ECG, and blood and urine sampling. Please see Table 1 for further details.

Please note that based on local Ethics Committees (ECs) or National Competent Authority requirements, additional diagnostic testing may be required for selected participants or selected centers to exclude tuberculosis (TB), Lyme disease, human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy (HAM), AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

4.1.2 Treatment Period

4.1.2.1 Double-Blind, Double-Dummy, Comparative Treatment Period

Eligible participants will be randomized via an interactive voice or web-based response system (IxRS) into 1 of 2 treatment groups: an ocrelizumab 600 mg regimen (Group A) or an IFN β-1a (Group B) regimen. See Table 7 and Table 11 for more details.

During the double-blind, double-dummy, comparative treatment period, participants will be assessed at clinical visits as per the schedule of activities (Table 1).

Before the next cycle of study drug, participants will be evaluated for pre-specified conditions and laboratory abnormalities to allow for re-treatment (see Section 6.1.4 for more details).

Participants who discontinue taking study medication within the 96-week, double-blind, double-dummy, comparative phase (treatment period) of the study will enter the safety follow-up period (see below); they will not be eligible for the OLE phase.

4.1.3 Open-Label Extension Phase Screening Period

Participants who complete the 96-week treatment period may become eligible for the OLE phase of the study. Participants will be consented for participation in the OLE phase if they may benefit from treatment with ocrelizumab. Participants who are not willing to participate in the OLE phase of the study will be entered into the safety follow-up period (see below). Participant treatment allocation during the double-blind, double-dummy, treatment period should not be unblinded regardless of participation in the OLE phase.

In the case of a participant who initially declines participation in the OLE phase and subsequently reconsiders the decision, the participant will have up to 24 weeks after the Week 96 visit to enter the OLE phase. In this instance, he or she should not have taken any prohibited medication as specified in Section 5.5.2.1. Participants who decline participation in the OLE phase should enter the safety follow-up period.

Participants who have consented to participate in the OLE phase will enter an OLE phase screening period to be evaluated for eligibility. The OLE phase screening period will start after all assessments at the Week 96 visit have been performed. This screening period will last up to 4 weeks. The OLE phase screening period could be longer than 4 weeks. If a prolongation of the OLE phase screening period is needed, it should be discussed with the Sponsor on a case-by-case basis.

Information from assessments performed during the Week 96 visit will be utilized to verify the eligibility of the participant for the OLE phase of the study. See Section 5.4.

During the OLE phase screening period, all participants should receive Rebif/Rebif placebo (depending on initial arm they were assigned to) until the first infusion of Cycle 5. See Table 7 and Table 11 for more details regarding the Rebif/Rebif placebo regimen.

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

4.1.4 Open-Label Extension Phase

Duration: the OLE phase will continue as per local regulation or should the Sponsor decide to terminate the ocrelizumab program for MS. Unless terminated earlier for any of the reasons mentioned above, 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.

Treatment: during the OLE phase, all participants will receive the ocrelizumab 600-mg dosing regimen every 24 weeks (see Table 6 and Section 5.17 for more details).

Withdrawal: participants who withdraw from the OLE phase will be entered into the safety follow-up period (see below).

4.1.5 Safety Follow-Up Period

Participants who discontinue treatment prematurely for any reason during the following periods will be entered into the safety follow-up period:

- Before completion of the 96-week double-blind, double-dummy, treatment period
- During the OLE phase screening period
- During the OLE phase
- Participants who choose not to enter the OLE phase or are not eligible for the OLE phase after completing the 96-week, double-blind, double-dummy, treatment period

In the OLE phase screening period, in the case of a participant who initially declines participation in the OLE phase and subsequently reconsiders the decision, the participant will have up to 24 weeks after the Week 96 visit to enter the OLE phase. In this instance, he or she should not have taken any prohibited medication as specified in Section 5.5.2.1.

The safety follow-up period will last *up to* 48 weeks starting from the date of the last infusion of ocrelizumab/ocrelizumab placebo. Safety follow-up visits will be performed at 12-week intervals starting from the date of the participant's last visit (the withdrawal from Treatment Visit). *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.*

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

During safety follow-up participants will be assessed at clinical visits every 12 weeks. Telephone interviews will be performed every 4 weeks.

Please see the schedule of activities (Table 2) for further details.

Table 5 Overview of Dosing Regimen in the Double-Blind, Double-Dummy, Treatment Period

	Double-Blind, Double-Dummy, Treatment Period [a, b]				
	1st Cycle [c] (Weeks 1–24)		2nd Cycle [c] (Weeks 24–48)	3rd Cycle [c] (Weeks 48–72)	4th Cycle [c] (Weeks 72–96)
Study Medication	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion
A Ocrelizumab 600 mg regimen	Ocrelizumab 300 mg IV		Ocrelizumab 600 mg IV		
B Rebif regimen [d]	Rebif SC 3 × week	→			

Please note: 100 mg of methylprednisolone IV will be administered in both treatment arms before each infusion of ocrelizumab/ocrelizumab placebo.

[a] The double-blind, double-dummy, treatment period consists of 96 weeks of treatment (4 treatment cycles).

[b] Each treatment cycle has a duration of 24 weeks. The first cycle consists of two 300-mg ocrelizumab IV infusions separated by 14 days. Cycles 2–4 consist of a single IV infusion of 600 mg ocrelizumab.

[c] Before each infusion, a clinical evaluation will be performed to ensure that the participant remains eligible for treatment.

[d] See Table 11 for the detailed Rebif dosing regimen.

Table 6 Overview of Dosing Regimen in the OLE Phase Screening Period and the OLE Phase

Study Medication	OLE Phase Screening Period	OLE Phase [a]				
		5th Cycle [b, c]		6th Cycle [b, c]	7th Cycle [b, c]	Nth Cycle [b–d]
		Day 1 Infusion	Day 15 Infusion			
Ocrelizumab 600-mg regimen	– [e]	Ocrelizumab 300 mg IV		Ocrelizumab 600 mg IV		
Rebif regimen	Rebif SC 3 × week [f]	– [g]				

OLE = open-label extension.

Please note: 100 mg of methylprednisolone IV and an oral or IV antihistamine (such as diphenhydramine 50 mg or an equivalent dose of an alternative) will be administered in both treatment arms before each infusion of ocrelizumab/ocrelizumab placebo.

[a] The OLE phase can terminate at any moment or cycle (see Section 4.1.9).

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

[c] Before each infusion, a clinical evaluation will be performed to ensure that the participant remains eligible for treatment.

[d] Each treatment cycle has a duration of 24 weeks. The first cycle of the OLE phase consists of two 300-mg ocrelizumab IV infusions separated by 14 days. Cycle 6 onwards consists of a single IV infusion of 600 mg ocrelizumab.

[e] During the OLE phase screening period, ocrelizumab will not be administered.

[f] See Table 11 for the detailed Rebif dosing regimen.

[g] During the OLE phase, Rebif verum or placebo will not be administered.

4.1.6 Rationale for Study Design

4.1.6.1 Rationale for the Use of an Active Comparator

The consensus in the MS research community is that the use of placebo in Phase III studies of participants with RMS is (except in exceptional circumstances) ethically indefensible because of the availability of established, effective therapies (Polman et al. 2008).

4.1.6.2 Rationale for Choice of Active Comparator

Interferon β-1-a 44 μg SC 3 × weekly (Rebif) has been chosen as the active comparator for the ocrelizumab in RMS, Phase III clinical program based on its consistent evidence of efficacy in reducing MRI activity, relapses, and disability progression in participants with relapsing forms of MS (see Section 2.1.5).

4.1.6.3 Rationale for Double-Blind, Double-Dummy Study Design

The use of a double-blind, double-dummy study design minimizes the potential for bias and safeguards the integrity of the clinical data generated from this study. Although this approach increases the participant's burden, this design reduces the risk of concluding that superiority to the active comparator was driven by participant and assessor bias. Regulatory agencies have mandated this study design be implemented throughout the Phase III clinical program. For additional measures intended to minimize bias, please see below.

4.1.6.4 Rationale for Choice of Study Population

This study plans to enroll participants with RMS who have an EDSS score of 0–5.5 at screening and who have had 2 documented clinical attacks within the previous 2 years or 1 clinical attack that occurred within the last year before screening. These criteria have been implemented to further characterize the benefits of treatment with ocrelizumab in a wide range of participants with RMS with varying degrees of disease activity and severity.

The age range will be limited to $\leq$55 years to avoid confounding by neurological conditions prevalent in older individuals, including but not limited to, microvascular disease.

Exclusion of participants in whom Rebif has failed or who cannot tolerate Rebif prevents these participants from being randomized to further Rebif therapy and reduces the potential for unbalanced dropout rates. Additional exclusion criteria relating to concomitant diseases, laboratory parameters, and previous medications help to ensure participant safety in the study. See Section 5.3 for more details.

4.1.6.5 Rationale for Study Endpoints

The proposed study endpoints are widely accepted as clinically relevant and have been used in numerous pivotal clinical trials in RMS. The primary endpoint for the study will be ARR over 96 weeks based on protocol-defined relapses. Key secondary endpoints will include the time to onset of confirmed disability progression, confirmed at scheduled clinic visits, for at least 12 weeks. Confirmed disability progression at 24 weeks will also be examined. Prevention of relapses as well as the prevention or delay of accumulation of sustained neurological disability are meaningful goals in the treatment of participants with MS.

4.1.6.6 Rationale for the Duration of the Double-Blind, Double-Dummy Treatment Period

The 96-week, double-blind, double-dummy treatment duration has been chosen to allow for the assessment of clinical efficacy and safety over 2 years of treatment, consistent with current regulatory guidelines.

4.1.6.7 Rationale for the Open-Label Extension Phase

Multiple sclerosis is a chronic disease that requires lifelong treatment to reduce the frequency of relapse and accumulation of disability. Once a participant is diagnosed with definite MS, accepted treatment guidelines propose that he/she be offered lifelong treatment because no evidence suggests that MS spontaneously remits (Rio et al. 2011).

Results of long-term, follow-up, exploratory studies suggest that exposure to DMT for more than 2 years improves outcomes by delaying the time to disability progression. Furthermore, accumulating evidence indicates that, in MS, inflammatory damage is a continuous process leading to demyelination and axonal transection and is the substrate of permanent disability in MS (Trapp et al. 1998; Lindberg et al. 2004; Freedman 2011).

Based on the long-term efficacy and safety data in Phase II Study WA21493/ACT4422G (for details, please see Section 2.1.4.1), it is justified to offer ocrelizumab to participants who would otherwise receive treatment that, in most cases, is modestly effective in reducing the frequency of relapses and in preventing sustained disability (Scalfari et al. 2010; Kappos et al. 2012).

Thus, participants who complete the 96-week, double-blind, double-dummy, treatment period will be offered the option to participate in an OLE phase of the study. Providing participants with the opportunity to prolong treatment with ocrelizumab beyond 2 years will provide more information on the long-term safety of ocrelizumab in RMS (e.g., the risk of infections/serious infections/opportunistic infections or potential loss of previously acquired immunity [e.g., hypogammaglobulinemia, specific serological titers]), as well as allow further collection of tolerability and efficacy information from participants with long-term exposure. Furthermore, the OLE phase will increase the overall number of participants exposed and participant-year exposure, thus increasing the likelihood of detecting rare events and the understanding of the safety/efficacy profile. Analyzing the long-term safety, tolerability, and efficacy of ocrelizumab is of critical importance to eventually help clinicians make informed decisions on therapy for participants (Day and Williams 2007).

4.1.6.8 Rationale for the Safety Follow-Up Period

Data collected during this period will allow for evaluation of B-cell repletion after stopping anti-CD20 treatment and allow collection of safety and efficacy data to document maintenance of the effect and/or the potential for a withdrawal effect.

4.1.6.9 Rationale for the Use of Methylprednisolone and Antihistamines

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 an equivalent dose of an alternative). 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. 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 USPI).

To mitigate the risk that even a low dose of methylprednisolone may have a small effect on the efficacy outcomes of the study, methylprednisolone will be administered to participants. It is of note that the dose of methylprednisolone used for premedication will be up to 50× smaller than that used for the symptomatic treatment of relapses in MS. In the event that methylprednisolone is contraindicated for the participant, an equivalent dose of an alternative steroid (e.g., dexamethasone) should be used as premedication before the infusion.

4.1.6.10 Additional Measures to Mitigate Bias

The use of HDHF IFN β as the active comparator for this study during the double-blind, double-dummy treatment period presents some difficulties for maintaining participant and physician blinding. See Section 2.1.5.

To prevent potential unblinding of the assigned arm in the double-blind, double-dummy, treatment period as a result of adverse events or changes to laboratory results, the following, additional measures have been implemented:

- **The Examining Investigator/EDSS assessor** will perform the neurological examination, document the Kurtzke Functional Systems (KFS) scores, and assess EDSS scores. During the double-blind, double-dummy, treatment period, the Examining Investigator/EDSS assessor and their qualified designees (if applicable) will not be involved with any aspect of medical management of the participant and will not have access to participant data. Every effort will be made to ensure that no change is made in the Examining Investigator/EDSS assessor throughout the course of the study for any individual participant. The Examining Investigator/EDSS assessors will be trained and instructed not to discuss what adverse effects (if any) the participant is experiencing from their medication. The Examining Investigator/EDSS assessors will receive training in performing EDSS assessments before the beginning of the study and must have successfully passed an examination on performance of the Neurostatus EDSS examination within 24 months of participation. All Examining Investigator/EDSS assessors will receive ongoing training on performance of the Neurostatus EDSS examination throughout the course of the study.
- **Participant education:** during the double-blind, double-dummy treatment period, before being examined by the Examining Investigator/EDSS assessor, participants will be instructed not to discuss what (if any) adverse effects they may be experiencing. Treating physicians and/or study coordinators should remind participants of these instructions before EDSS assessments, and this should be documented in the source documents.

- **Blinded, central MRI assessments:** during the double-blind, double-dummy, treatment period, a blinded, central, MRI reader will assess all MRI scans done during the study. These assessments will provide independent confirmation of the relative changes in immune-mediated, CNS damage.
- **Blinding of laboratory parameters:** laboratory parameters that may lead to unblinding to treatment assignment, such as fluorescence-activated cell sorting (FACS) cell counts including CD19+ cells, lymphocyte count, IgM and IgG levels, and type I IFN neutralizing antibody levels, will be blinded for all participants, except those meeting unblinding criteria for safety reasons. These laboratory parameters will remain blinded during the double-blind, double-dummy treatment period, safety follow-up period, the OLE phase screening period, and during the first cycle of the OLE phase (Cycle 5).

4.1.7 Rationale for Dose Selection

The dose for the ocrelizumab Phase III clinical program was chosen to bring the community with MS significant improvement in clinical efficacy vs. that for the current standard of care, with acceptable safety. The dose of ocrelizumab in the Phase III clinical program is 600 mg ocrelizumab every 24 weeks (administered as dual infusions of ocrelizumab 300 mg on Days 1 and 15 of the first 24-week treatment cycle, and 600 mg on Day 1 of each 24-week treatment cycle thereafter). This dose has been established as the lowest, maximally effective dose based on the results from Study WA21493/ACT4422g. The safety of this dose has substantial support from the Phase III clinical program in rheumatoid arthritis (RA), an analogous, although systemic autoimmune disease, in a population at greater risk.

Study ACT2847g was a Phase I/II, dose escalation study in participants with RA that examined 5 dosing regimens. In Study ACT2847g, the 2 lowest dose groups (receiving less than 200 mg×2) demonstrated reduced clinical benefits on some endpoints, earlier return of peripheral B cell counts, and higher rates of immunogenicity. In the RA Phase III program, with the exception of participants recruited from Asia, the dose of 200 mg×2 established a safety profile comparable with that for placebo. The higher dose of 500 mg×2 demonstrated apparently superior efficacy, especially in its effects on "high-hurdle" clinical endpoints and joint preservation, based on X-ray imaging.

In the population with MS (Study WA21493/ACT4422g), 2 doses of ocrelizumab were studied, 2000 mg (administered as dual 1000 mg infusions on Days 1 and 15 of the first, 24-week treatment cycle) and 600 mg (administered as dual 300 mg infusions on Days 1 and 15 of the first treatment cycle). Pre-specified primary and secondary efficacy analyses for Study WA21493/ACT4422g indicated that 300 mg×2 of ocrelizumab is highly effective in suppressing MRI lesion activity and reducing the risk of clinical relapses in participants with RRMS over 24 weeks. No difference in efficacy was seen between the ocrelizumab 1000 mg×2 and 300 mg×2 doses in terms of either MRI or clinical endpoints in the intent-to-treat (ITT) study population. However, exploratory

analyses stratifying groups according to baseline MRI activity suggest superior efficacy with 1000 mg × 2 versus 300 mg × 2 at 24 weeks in participants with MRI activity at baseline (≥ 4 enhancing lesions). Similarly, in these participants, the 1000 mg × 2 dose was apparently more effective than the 300 mg × 2 dose at Week 24 and (to a lesser extent) at Week 48 in reducing the absolute number of clinical relapses. Neither the MRI nor the clinical efficacy differences are statistically significant; however, these results suggest reduction of clinical efficacy at lower doses in participants with active MS. This apparent dose effect was seen even though linear kinetics (so that complete receptor occupancy can reasonably be assumed) and near-complete peripheral CD19 suppression were observed for both doses. Nonclinical studies in primates have shown differential susceptibility of tissue resident vs. circulating B cell populations in response to anti-CD20 antibodies (Gong et al. 2005; Ahuja et al. 2007; Kap et al. 2010). Because tissue resident B cell populations are beyond our ability to measure directly, peripheral CD19 count is likely to be a sensitive but non-specific PD marker for anti-CD20 efficacy.

4.1.7.1 Conclusion

Based on available data, the dose of 600 mg of ocrelizumab IV (given as dual infusions of 300 mg 14 days apart for the first 24 weeks and a single infusion of 600 mg every 24 weeks thereafter) is the most likely the dose that is able to demonstrate robust clinical efficacy, an acceptable safety profile, and a low risk of immunogenicity, thereby maximizing the likelihood of significant benefit vs. that for standard of care in participants with RMS.

4.1.8 End of Double-Blind, Double-Dummy, Treatment Period of the Study

The end of the double-blind, double-dummy, treatment period of the study is defined as the date at which the last data point during double-blind, double-dummy treatment from the last participant is received, as required for statistical analysis defined in the Statistical Analysis Plan (SAP).

To maintain the integrity of the study data, all study sites and all EDSS assessors will remain blinded to participant treatment allocation until approximately 24 weeks after the Week 96 visit of the last participant randomized to allow the confirmation of the last 24-week confirmed disability progression event (see Section 8.2).

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

Approximately 800 participants (400 per treatment arm) will be recruited over a planned recruitment period of 16 months.

Participants will be randomized in 2 groups in a 1:1 ratio. An independent IxRS provider will conduct randomization and hold the treatment assignment code. Participants will be stratified by region (United States vs. Rest of World [ROW]) and baseline EDSS (<4 and ≥ 4).

4.3 CENTERS

This will be a multicenter, international study. It is anticipated that approximately 220 centers worldwide will participate.

5. STUDY POPULATION

Under no circumstances are participants who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

5.1 OVERVIEW

Adult participants with RMS who fulfill the eligibility criteria specified in Sections 5.2 and 5.3 are eligible for enrollment in the study. For the eligibility criteria for the OLE phase, please see Section 5.4.

5.1.1 Recruitment Procedures

Sites are encouraged to identify participants for potential recruitment with use of pre-screening enrollment logs or a pre-identification website.

Participants who are candidates for enrollment into the study will be evaluated for eligibility by the investigator to ensure they fulfill eligibility criteria (see Sections 5.2 and 5.3).

All participants must sign the Informed Consent Form before screening and before any changes to their existing medication for the purposes of enrollment in the trial.

No participant may begin treatment prior to randomization and assignment of a medication number. Under no circumstances are participants who enroll in this study 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.

No replacement for participants who withdraw from the study after randomization is planned.

5.2 INCLUSION CRITERIA

Participants must meet the following criteria for study entry:

- Ability to provide written, informed consent and be able to follow the schedule of protocol assessments

  Participants who are unable to complete exploratory assessments (e.g., electronic participant-reported outcomes [ePROs]) because of physical/disease limitations will not be excluded from the study.
- Age 18–55 years, inclusive, at screening
- Diagnosis of MS, in accordance with the revised McDonald criteria (Polman et al. 2011)
- At least 2 documented clinical attacks within the last 2 years before screening, or 1 clinical attack in the year before screening (but not within 30 days before screening)
- Neurological stability for ≥30 days before both screening and baseline
- EDSS score from 0–5.5, inclusive, at screening
- Documented MRI of brain with abnormalities consistent with MS before screening
- Participants of reproductive potential must use 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 their 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]).

    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 follicle-stimulating hormone [FSH]).
- For participants of non-reproductive potential (adherence to local requirements, if more stringent, is required):
  - Women may be enrolled if postmenopausal (i.e., spontaneous amenorrhea for 12 months confirmed by a FSH level >40 mIU/mL, unless the participant is

receiving a hormonal therapy for menopause or is surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy)

- Men may be enrolled if they are surgically sterile (have been castrated)

5.3 EXCLUSION CRITERIA

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

- Diagnosis of PPMS
- Disease duration of more than 10 years in participants with an EDSS $\leq$ 2.0 at screening
- Inability to complete an MRI (contraindications for MRI include but are not restricted to weight $\geq$ 140 kg, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks before the time of the intended MRI, etc.)
  - Participants with contraindication to Gd can be enrolled in the study but cannot receive Gd contrast dyes during MRI scans.
- Known presence of other neurological disorders that may mimic MS, including but not limited to, neuromyelitis optica, Lyme disease, untreated vitamin B12 deficiency, neurosarcoidosis, and cerebrovascular disorders

5.3.1 Exclusions Related to General Health

- Pregnancy or lactation
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History or currently active primary or secondary immunodeficiency
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant or uncontrolled somatic disease or any other significant disease that may preclude participation in the study
- Congestive heart failure (New York Heart Association III or IV functional severity)
- Known active bacterial, viral, fungal, or mycobacterial infection or other infection, excluding fungal infection of nail beds
- Infection requiring hospitalization or treatment with IV antibiotics within 4 weeks before baseline visit or oral antibiotics within 2 weeks before baseline visit
- 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 in Germany 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 before enrollment into the study. If a tuberculin skin test is performed, an induration of >6 mm is a positive result for a participant with history of having received Bacille Calmette-Guérin (BCG) vaccine, whereas an induration of >10 mm is a positive result for a participant without a history of having received BCG vaccine.

If necessary, a QuantiFERON-TB Gold test might be complemented by additional specific diagnostic tests according to standard procedures in Germany.

- History of PML
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins
- History of alcohol or drug abuse within 24 weeks prior to baseline
- History or laboratory evidence of coagulation disorders

5.3.2 Exclusions Related to Medications

Participants screened for this study should not be withdrawn from therapies for the sole purpose of becoming eligible for the trial. Participants who discontinue their current therapy for non-medical reasons should specifically be informed of their treatment options before deciding to enter the study.

Exclusion related to medications include the following:

- Receipt of a live vaccine within 6 weeks before the baseline visit

  In rare cases when a participant requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks.
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer; or treatment with any experimental procedures for MS [e.g., treatment for chronic cerebrospinal venous insufficiency])
- Contraindications to or intolerance of oral or IV corticosteroids, according to the country label, including:
  - Psychosis not yet controlled by a treatment
  - Hypersensitivity to any of the constituents
- Contraindication to Rebif or incompatibility with Rebif use, including:
  - Current severe depression and/or suicidal ideation
  - Hypersensitivity to natural or recombinant IFN-β, or to any excipients
  - Previous suboptimal response to HDHF IFN or cessation of HDHF IFN therapy due to poor tolerability

- Prior cessation of Rebif® therapy due to toxicity, which is likely to recur

- Treatment with dalfamipridine (Ampyra®) unless receiving a stable dose for ≥30 days before screening. Whenever possible, participants should continue to receive stable doses throughout the 96-week treatment period.
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- 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 MS before screening. For a participant to be eligible, systemic corticosteroids should not have been administered also between screening and baseline.
- Any previous treatment with Campath® (alemtuzumab), anti-CD4, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, MTX, or natalizumab within 24 months before screening.

  Note: Participants previously treated with natalizumab will be eligible for this study only if the duration of treatment with natalizumab was <1 year.
- Treatment with fingolimod or other S1P receptor modulator (i.e., BAF312) or with BG12 within 24 weeks before screening

  Note: Only participants with T lymphocyte count ≥LLN will be eligible for this study.
- Treatment with immunoglobulin IV within 12 weeks prior to baseline

5.3.3 Exclusions Related to Laboratory Findings

Retesting before baseline: in rare cases in which the screening laboratory samples are rejected by the central laboratory (i.e., because of a hemolyzed sample) or the results are not assessable (i.e., indeterminate) or abnormal, the tests need to be repeated within 4 weeks. Any abnormal screening laboratory value that is clinically relevant should be retested 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 should not exceed 8 weeks.

Exclusions related to laboratory findings include the following:

- Positive serum β-human chorionic gonadotropin (hCG) measured at screening
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or total positive hepatitis B core antibody [HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb)
- Positive rapid plasma reagin (RPR)
- CD4 count <300/μL
- AST/SGOT or ALT/SGPT ≥2.0×ULN

- Platelet count $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)
- 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)
- Total neutrophil count $< 1.5 \times 10^3/\mu L$

Please note: based on local ECs or National Competent Authority requirements, additional diagnostic testing may be required for selected participants or selected centers to exclude TB, Lyme disease, HAM, 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 96-week, double-blind, double-dummy, treatment period, and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab
- Are able and willing to provide written informed consent for the OLE phase (e.g., before the first infusion at Cycle 5) and to comply with the study protocol
- Be willing to comply with the following contraception requirements:
  - Female participants who are of reproductive potential and sexually active must continue use of a reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, is required)

    One primary method of contraception is to be used 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 participants without reproductive potential
  - Women may be enrolled if postmenopausal (i.e., have had spontaneous amenorrhea for the last year 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., have had a hysterectomy and/or a complete bilateral oophorectomy)
- Meet re-treatment criteria with ocrelizumab (see Section 6.1.4)

5.5 CONCOMITANT MEDICATION AND TREATMENT

5.5.1 Definition of Concomitant Treatment

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

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 form of electronic Case Report Forms (eCRFs) starting from the baseline visit (including medication and procedures taken between screening and baseline). Medications taken for the treatment of MS in the 2-year period before the baseline visit and medications taken for the symptoms of MS in the 3-month period before the baseline visit will be recorded at the baseline visit. Additionally, medications and medical/surgical procedures administered for any non-MS condition within 12 months before the baseline visit will also be recorded at the baseline visit.

5.5.2 Treatment for Symptoms of Multiple Sclerosis

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. During the OLE phase of the study, initiation of therapy with Ampyra® (dalfampridine) is allowed, if indicated by the treating physician.

Treatment of relapses: participants who experience a relapse during the double-blind, double-dummy, treatment period, OLE phase screening period, or the OLE phase may receive treatment with oral or IV corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 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 for further details).

5.5.2.1 Prohibited Concomitant Treatments for Multiple Sclerosis

Therapies for MS noted in the exclusion criteria under "Exclusions Related to Medications" (Section 5.3) are not permitted during the double-blind, double-dummy, treatment period, the OLE phase screening period, or the OLE phase with the exception of systemic corticosteroids for the treatment of a relapse; IV Ig is also permitted. For participants who withdraw from treatment with ocrelizumab and enter safety follow-up, alternative treatments for MS judged clinically appropriate by the Treating Investigator are allowed. However, because sufficient data are not available to inform 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 *or another DMT* will discontinue participation in the study completely and will not enter or continue in the safety follow-up period.

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. The detailed Study BN29739 results can be found in the current version of the IB.

A recent integrated analysis of participants with MS treated with ocrelizumab revealed that after treatment with ocrelizumab over 2 years, the proportion of participants with positive antibody titers against *Streptococcus pneumoniae*, mumps, rubella, and varicella was generally similar to the proportion at baseline.

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. Known dates of immunizations will be recorded on specific eCRF pages. **Immunizations should be completed at least 6 weeks before the first administration of ocrelizumab.**

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

The safety of immunization with live viral vaccines after 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 before the first dosing (see exclusion criteria, Section 5.3), during ocrelizumab treatment, and for as long as the participant is B-cell depleted.

For details regarding vaccinations during ocrelizumab treatment, please see the current version of the Ocrelizumab IB.

5.6 CRITERIA FOR PREMATURE WITHDRAWAL

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

Participants must be withdrawn from treatment (regardless of whether they are in the double-blind, double-dummy, 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
- Participants who demonstrate active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B
- Participants with PML
- Participants with elevation in level of ALT $\geq 10 \times$ ULN, jaundice, or other clinical symptoms of liver dysfunction (please see Section 6.2.2 for more details)

  Only applicable during the double-blind, double-dummy, treatment period
- Participants with persisting elevation of ALT $> 3 \times$ ULN, or other clinical symptoms of liver dysfunction that did not resolve with Rebif/Rebif placebo dose modification (please see Section 6.2.2 for more details)

  Only applicable during the double-blind, double-dummy treatment period
- 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

Participants who withdraw during the double-blind, double-dummy, treatment period, OLE phase screening period, or the OLE phase, for any reason, should complete the safety follow-up period. If the participant insists on discontinuing participation in 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, for lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), because of a cure, or for any reason that leads the investigator to conclude 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. If possible, the participant should be followed up until the adverse event has resolved.

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 before withdrawal as thoroughly as possible.

Please note: 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 (48 weeks following the last infusion).

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

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

5.6.1 Withdrawal of Participants from the Roche Clinical Repository

Participants who gave consent to provide Roche Clinical Repository (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 Roche in writing of the participant's wishes by with use of the RCR Participant Withdrawal Form and enter the date of withdrawal in the participant's eCRF. A participant's withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR; likewise, a participant's withdrawal from the RCR does not constitute a withdrawal from the main trial (see Section 5.12).

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 5.12).

5.6.3 Participant Agreement for Continuation in the Study (in Case of Confirmed Disability Progression)

During the double-blind treatment period, in the event of confirmed disability progression on EDSS confirmed 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 alternative treatment options available for that participant. The result of this discussion must be included in the participant's file, prior to any further dosing of study medication.

If after the discussion, the participant decides not to continue with the study treatment, they should be discontinued from any further treatment, complete applicable Withdrawal from Treatment Visit procedures and be entered into the safety follow-up period.
For definition of confirmed disability progression, please see Section 5.10.2.2.

5.7 REPLACEMENT POLICY (ENSURING ADEQUATE NUMBERS OF EVALUABLE PARTICIPANTS)

5.7.1 For Participants

Participants prematurely discontinued from the study for any reason will not be replaced.

5.7.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment
- Poor protocol adherence
- Sponsor's discretion (Sponsor refers to F. Hoffmann-La Roche, Ltd and Genentech, Inc.)

5.8 SCREENING EXAMINATION AND ELIGIBILITY SCREENING FORM

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

Consenting participants will enter the 2-week screening period to be evaluated for eligibility (Table 1). Participants must fulfill all entry criteria for participation in the study.

The screening period can be extended to a total period of 8 weeks in cases when a laboratory blood test or MRI scan needs to be repeated for confirmation during the screening interval, or for other relevant clinical, administrative, or operational reasons.

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

An Eligibility Screening Form (ESF) 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 reasons must be 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 all eligibility criteria, he or she will be randomized via IxRS to 1 of 2 treatment groups: ocrelizumab 600 mg (300 mg × 2 given 14 days apart for the first 24 weeks and 600 mg × 1 every 24 weeks thereafter) or Rebif.

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 the 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 DURING THE DOUBLE-BLIND, DOUBLE-DUMMY TREATMENT PERIOD

This is an assessor blinded study. During the double-blind, double-dummy treatment period, each site will have 2 investigators: a Principal (Treating) Investigator and an Examining Investigator or rater.

- **The Treating Investigator** is the physician responsible for participant care and should be a neurologist experienced in the care of participants with MS. The Principal Investigator will have access to safety and blinded 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 Neurostatus Functional Systems Scale (FSS) and EDSS examination prior to study start

The Examining Investigator will perform the neurological examination, document the FSS scores, and assess EDSS scores and the Karnofsky Performance Status Scale. The Examining Investigator or a qualified designee will also be responsible for performing and documenting results from the following: MSFCS, low-contrast visual acuity testing, and the SDMT. They will only have access to data from the assessments listed above. Every effort will be made to ensure that there is no change in the EDSS rater throughout the course of the study for any individual participant. Whenever possible, the same person should perform the examination for the full study duration.

All efforts should be made to keep the Examining Investigator blinded to the treatment assignment during the double-blind, double-dummy treatment period. 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 for Treating and Examining Investigator.
The Treating Investigator and the Examining Investigator will not be allowed to switch roles.

5.10.1 Overview of Clinical Visits During the Double-Blind, Double-Dummy Treatment Period

After the screening visit, participants fulfilling the entry criteria will be scheduled for the baseline assessments. Randomization will occur only after the participant meets all inclusion and exclusion criteria on Day 1. Visits will take place as described in the schedule of activities (Table 1).

Visits should be scheduled with reference to the date of the baseline visit (Day 1). A minimum interval of 20 weeks kept between the ocrelizumab/ocrelizumab placebo second infusion of Cycle 1 (i.e., infusion Week 2) and the next infusion on Cycle 2 (Week 24). A minimum of 22 weeks must occur between ocrelizumab/ocrelizumab placebo single infusions administered during Weeks 24, 48, and 72.

At infusion visits, participants treated with ocrelizumab/ocrelizumab placebo should remain in observation for at least 1 hour after the completion of the infusion.

If for logistical reasons the ocrelizumab/ocrelizumab placebo infusion at Week 24, 48, or 72 cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the participant still meets re-treatment criteria (see Section 6.1.4).

Participants who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 5.10.1.1). Additional unscheduled visits for the assessment of potential relapses, new neurological

symptoms, safety events or for dispensing Rebif/Rebif placebo if down-titration is needed may occur at any time.

5.10.1.1 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in schedule of activities (Table 1). 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. Delayed dosing visit should not be scheduled for the first infusion of the first treatment cycle (Day 1), as treatment with the first study drug infusion should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing; see Section 5.9).

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 (±2 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 infusions administered during Weeks 24, 48, and 72.

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.

5.10.1.2 Unscheduled Visits

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

Participants with new neurological symptoms suggestive of relapse should have an EDSS performed by Examining Investigator, whenever possible within 7 days of the onset of the relapse. Other tests/assessments may be done as appropriate.
Please note: if during the double-blind, double-dummy treatment period, Rebif/Rebif placebo dose modification is necessary in case of ALT elevations, then unscheduled visits may be required for dispensing of study medication (see Section 6.2).

Please see Section 7.3.5.1 for guidance on the diagnosis of PML.

5.10.1.3 Withdrawal Visits in the Double-Blind, Double-Dummy Treatment Period

At the moment a participant meets one or more of the withdrawal criteria (Section 5.6), this participant is regarded withdrawn from treatment. Participants who withdraw from

ocrelizumab treatment will need to complete all assessments as shown in schedule of activities and will enter the safety follow-up period.

At the termination of the study (see Section 4.1.9 for definition of end of the study), 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 the schedule of activities, Table 3. Thereafter, all participants will be treated according to individual center practice.

For participants who have withdrawn from the double-blind, double-dummy treatment period, OLE phase, the OLE phase screening period, 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 (for example, 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 5.5.2.1 for recommendations on alternative treatments for MS).

Please note: at the withdrawal from double-blind, double-dummy treatment period visit or OLE phase, an MRI scan will be required only if not performed in the prior 4 weeks.

5.10.2 Assessment of Efficacy

5.10.2.1 Assessment of Relapse

All new or worsening neurological events consistent with MS representing a clinical relapse are to be reported on the dedicated page of 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).

Protocol-defined relapse is the occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications) and immediately preceded by a stable or improving neurological state for at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate 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: Sexual dysfunction and Fatigue will not be scored. Please note: adjudication of protocol-defined relapses will be performed by the Sponsor based on pre-specified criteria, applied to data collected by investigator, in a blinded fashion.

All participants with new neurological symptoms suggestive of a relapse should be referred to the Examining Investigator for EDSS assessment, whenever possible within 7 days of the onset of the relapse. Any participant, complaining of a neurological symptom, defined at a visit or over the phone, should be referred to the Examining Investigator unless the Principal Investigator determines that the symptom is due to mitigating circumstances (such as an intensification of neurological symptoms from a transient systemic infection).

Please note: clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded on a pre-specified eCRF "MS Relapse" electronic form (eForm). Multiple sclerosis relapses should not be reported on the Adverse Event eForm eCRF.

5.10.2.2 Assessment of Disability

Disability progression has been defined as an increase of ≥ 1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. Disability progression is considered confirmed when the increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks, after the initial documentation of neurological worsening.

Confirmed disability progression, confirmed for 12 weeks, after the initial documentation of neurological worsening, will be analyzed as key secondary endpoint.
Additionally, confirmed disability progression for 24 weeks will be assessed. The initial event of neurological worsening must occur during the 96-week, double-blind, double-dummy, treatment period.

5.10.2.3 Kurtzke Expanded Disability Status Scale

The EDSS (Cohen et al. 2000) is based on a standard neurological examination, incorporating the following functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental]) and ambulation rated and scored as FSS. Each FSS is an ordinal clinical rating scale ranging from 0–5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death).

The EDSS will be assessed by the Examining Investigator. **All participants with new neurological symptoms suggestive of relapse should have an EDSS performed during an unscheduled visit whenever possible within 7 days of symptom onset.**

5.10.2.4 The Multiple Sclerosis Functional Composite Scale

The MSFCS consists of 3 subscales, including the 9-HPT, PASAT, and the T25FWT, which provide a global quantitative estimate of MS disability progression (Fischer et al. 1999).

The MFSCS will be performed by the Examining Investigator or a qualified designee who must remain blinded to the treatment assignment.

5.10.2.5 Low-Contrast Visual Acuity Testing

Low-contrast letter acuity charts (Sloan charts) have gained validity in the assessment of visual dysfunction in participants with MS not readily apparent on commonly used high-contrast acuity tests. Reductions in low-contrast letter acuity are associated with MS and correlate with increasing disability, MRI abnormalities, and reduced RNFL thickness as measured by OCT.

Low-contrast visual acuity testing will be performed with use of low-contrast letter acuity charts (low-contrast Sloan letter charts) by the Examining Investigator or a qualified designee at the timepoints indicated in the schedule of activities (Table 1).

5.10.2.6 The Symbol Digit Modalities Test

The SDMT has demonstrated sensitivity in detecting not only the presence of cognitive impairment, but also changes in cognitive functioning over time and in response to treatment. The SDMT is brief, easy to administer, and involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses can be written or oral, and for either response mode, administration time is just 5 minutes.

The SDMT will be administered by the Examining Investigator or a qualified designee at the timepoints indicated in the schedule of activities (Table 1 and Table 3).

5.10.3 Brain Magnetic Resonance 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 as detailed in the schedule of activities (Table 1). In addition, brain MRI scans will be obtained in participants withdrawn from the double-blind, double-dummy treatment period (at the withdrawal visit) if not performed during the previous 4 weeks.

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

- "Baseline" MRI should be performed after screening visit, but at least 10 days prior to the baseline visit
- MRI at visits scheduled at Weeks 24, 48, 96 or at the withdrawal visit (if applicable) should be performed within a window of ±4 weeks of the scheduled visit
- In the OLE phase, MRI should be performed yearly (e.g., Cycles 7, 9, etc.) within a window of ±4 weeks of the scheduled visit

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.

Magnetic resonance imaging 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 Acquisition Procedures Manual.

All MRI scans will also be reviewed locally by a radiologist for safety. During the double-blind, double-dummy treatment period, the MRI scan report containing only non-MS pathology will be provided to the Treating Investigator (see Section 5.10 for definition). At the investigational site, only the local radiologist/technician assigned to this study may have access to the MRI scans post-randomization;
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 that during the OLE phase, it is possible for the Treating Investigator to have access to MRI scans performed during the OLE phase.

5.10.4 Safety

Adverse events, vital signs, weight, physical and neurological examination, clinical laboratory tests (including pregnancy tests), 12-lead ECG, locally reviewed MRI for safety (non-MS CNS pathology), and data on concomitant medications and diseases will be collected throughout the study.

Please note: On the infusion days, the vital signs should be taken within 45 minutes prior to the methylprednisolone infusion in all participants. In addition, the vital signs should be obtained prior to the study drug infusion, then every 15 minutes (±5 minutes) for the first hour; then every 30 minutes (±10 minutes) until 1 hour after the end of the infusion. On 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 infusion-related reaction or if clinically indicated and should be recorded on the unscheduled vital signs eCRF.

Please see relevant sections of protocol for more details.

5.10.4.1 Electrocardiogram

A 12-lead ECG should be taken at the visits indicated in the schedule of activities (Table 1 and Table 3). 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.

5.10.4.2 Physical Examination

The physical examination will be performed as per schedule of activities. Diagnosis of new abnormalities or clinically significant worsening of preexisting abnormalities should be recorded as adverse events if appropriate.

5.10.4.3 Neurological Examination

A neurological examination will be performed at every planned visit and at unscheduled visit if applicable.

- In the presence of newly identified or worsening neurological symptoms at any given time in the study (double-blind treatment, safety follow-up, or the OLE period), a neurological evaluation should be scheduled promptly. In case of events suggestive of relapse, the Treating Investigator should request EDSS to be performed by the Examining Investigator, whenever possible within 7 days of the onset of the relapse.

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 7.3.5.1 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 7.3.5.1). The Sponsor's Medical Responsible and Medical Monitor should be contacted by e-mail. In addition, Sponsor medical responsible person should be immediately contacted by phone.

A participant with confirmed PML should be withdrawn from treatment.
Progressive multifocal leukoencephalopathy should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see Section 7.1.1.3).

5.10.4.4 Telephone Interviews

The purpose of this semi-structured interview is 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). The telephone interview will be conducted by site personnel familiar with the participant(s) every 4 weeks (±3 days) between the study visits during the double-blind, double-dummy treatment period, OLE phase screening period, OLE phase, and throughout the entire safety follow-up period.

The site will record in the eCRF the telephone interview as "Done" or "Not Done" and documentation of the interview will be maintained in the participant's study file.

Please see Appendix 4 for detailed information.

5.10.4.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used during the double-blind, double-dummy treatment period and the OLE phase screening period for prospective suicidality assessment. The C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the treatment.
The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The scale will be administered by the Principal Investigator or a qualified designee at the timepoints indicated in the schedule of activities. The C-SSRS "baseline" will be collected at baseline and the C-SSRS "since last visit" will be collected at subsequent visits.

Please note: assessing the risk of suicide is a difficult and complex task when applied to the individual participant. Certainly, no single clinical scale can replace a thorough medical examination and suicide risk assessment. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

5.10.5 The Karnofsky Performance Scale (Clinician-Reported Version)

The Karnofsky Performance Scale score allows participants to be classified as to their functional impairment. This scale is usually used to compare effectiveness of different therapies and to assess the prognosis in individual participants. The lower the Karnofsky score, the worse the survival for most serious illnesses.

The scale will be administered by Examining Investigator at the timepoints indicated in the schedule of activities (Table 1).

5.11 LABORATORY ASSESSMENTS

Roche Clinical Repository biomarker samples will be shipped directly to Roche Clinical Sample Operations unit. All other laboratory samples collected during the study will be shipped to central laboratory.

The procedures for the collection, handling and shipping of laboratory samples are specified in the Laboratory Manual.

The samples for this study should be classified, packed and shipped as UN3373 Biological Substance, Category B.

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

During the double-blind treatment period of the study, the total volume of blood loss for laboratory assessments will be approximately 341 mL over 2 years. The amount of blood taken at each visit will vary, but will be no more than 56 mL. During the OLE phase and in the safety follow-up period, the amount of blood taken at each visit will be no more than 41 mL.

5.11.1 Standard Laboratory Assessments

Please note: Some laboratory parameters that could reveal participant's allocation to study treatment, such as FACS cell counts, absolute neutrophil counts, Ig levels, and type I IFN neutralizing antibody levels, will be blinded. In order to ensure participants' safety in the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and Medical Monitors with reflex messages triggered by critical blinded laboratory results. Investigators notified of their participant's critical laboratory test results will be instructed to suspend further treatment with study drug until the participant becomes eligible for re-treatment. The reflex messages from a central laboratory, together with non-blinded laboratory results, should be carefully reviewed at every visit before continuing with study treatment. The reflex messages will occur during the double-blind, double-dummy treatment period until the fifth cycle (first cycle of OLE phase). The reflex messages will not be in effect from the sixth cycle onward. Further details will be provided in Laboratory Manual.

- **Hematology:** hemoglobin, hematocrit, RBC, WBC (absolute and differential), absolute neutrophil count, and quantitative platelet count
- **Blood chemistry:** AST/SGOT, ALT/SGPT, gamma glutamyl transferase (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 will be tested at screening, and yearly during the double-blind, double-dummy treatment period. Thyroid autoantibodies will be assayed only at screening.

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

- Total B cells ($CD19^{pos}$)
- Total T cell ($CD3^{pos}$)
- T helper cells ($CD3^{pos}$, $CD4^{pos}$)
- T_{CTL} ($CD3^{pos}$, $CD8^{pos}$)
- Natural killer cells ($CD3^{neg}$, $CD16/56^{pos}$)
- B-cell subsets:
  - Memory B cells ($CD19^{pos}$, $CD27^{pos}$, $CD38^{neg}$)
  - Naïve B cells ($CD19^{pos}$, $CD27^{neg}$, IgD^{pos})
  - Plasmablasts ($CD19^{lo}$, $CD27^{pos}$, $CD38^{hi}$)
- **Quantitative Immunoglobulin:** Ig levels (including Total Ig, IgG, IgM, and IgA isotypes)
- **Antibody titers:** measurement of antibody titers to common antigens (mumps, rubella, varicella, S. pneumoniae) will be performed. This information is used to assess the effect of ocrelizumab on specific humoral immunity to bacterial and viral antigens.
- **Human anti-human antibody (HAHA):** serum samples will be collected for determination of antibodies against ocrelizumab (HAHA; also known as an anti-drug antibody [ADA]). Since ocrelizumab concentrations affect the HAHA assay, the concentration of ocrelizumab will be measured as well at all timepoints with HAHA assessment to enable interpretation of the results (PK sample). For details please see the schedule of activities. 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.
- **Pregnancy test**: all women of childbearing potential must have regular pregnancy tests. At screening, a serum pregnancy test will be performed in central laboratory. During the double-blind, double-dummy treatment period and safety follow-up, a urine pregnancy test (sensitivity of at least 25 mIU/mL β-hCG) will be performed locally at the timepoints shown in schedule of activities (Table 1). On infusion visits, the urine pregnancy test should be performed prior to the methylprednisolone infusion. A positive urine pregnancy test should be confirmed with a serum test through the central laboratory prior to any further dosing with ocrelizumab.

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

5.11.2 Hepatitis Screening and Liver Function Monitoring

Participants with recurrent or chronic hepatitis B or history/presence of hepatitis C infection 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 viral DNA checked regularly as per the schedule of activities. 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+ test should be referred to a hepatologist for immediate assessment. 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, 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.

Please see Section 6.2.2 for further guidelines on liver function monitoring.

5.11.3 Plasma and Urine Banking for JC 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 case (see Section 7.3.5.1). Plasma samples (5 mL) and urine samples (10 mL) will be collected as per schedule of activities. As the assay of the virus DNA 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 collected for JCV analysis

(see Section 7.3.5.1). For details, please refer to the most up-to-date Laboratory Manual providing storage conditions and shipment instructions.

5.11.4 Pharmacokinetic/Pharmacodynamic Assessments

Blood samples will be collected to evaluate the PK and PD of ocrelizumab as described in the schedule of activities (Table 1). The blood volume collected for PK assessments will be approximately 2 mL per sample. These samples will be assayed for ocrelizumab concentration with use of an enzyme-linked immunosorbent assay.

Serum samples for determination of ocrelizumab concentrations will be collected at the timepoints detailed in the schedule of activities (Table 1). On the infusion visit at Week 72, two serum samples should be collected, one sample 5–30 minutes prior to the methylprednisolone infusion and the second sample 30 minutes (±10 minutes) following the completion of the ocrelizumab infusion. For all other infusion visits, a blood sample should be taken 5–30 minutes before the methylprednisolone infusion. At other times (non-infusion visits), samples may be taken at any time during the visit.

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 post-dose.

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

5.11.5 Type I Interferon Neutralizing Antibody Assay

Type I IFN neutralizing antibody assay will be performed during the double-blind, double-dummy treatment period (Table 1).

5.12 OPTIONAL SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

If the participant provides consent (see Section 5.12.5), 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.

5.12.1 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. The RBR 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

5.12.2 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 Informed Consent Form 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 5.12) will not be applicable at that site.

5.12.3 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 Informed Consent Form and applicable laws (e.g., health authority requirements).

5.12.4 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 Informed Consent Form (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.

5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each 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.

5.12.6 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.

5.12.7 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 Informed Consent Form. 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.

5.13 PROTEIN BIOMARKER SAMPLES

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 relapsing MS 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 will include, but are not limited to, interleukin-6.

A 6 mL sample of whole blood will be collected in a plain tube without EDTA for serum isolation. For sampling procedures, storage conditions and shipment instructions see study Sample Handling and Logistics Manual, which will be provided to each study site.

Blood specimens for protein biomarker discovery and validation will be collected from all participants as per 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.

5.14 PARTICIPANT-REPORTED OUTCOMES

Participant-reported outcomes data will be collected at the study visit with an electronic tablet device during the double-blind, double-dummy treatment period. The tablet with the participant-reported outcome (PRO) instruments will be distributed by the investigator staff and completed in their entirety by the participant.

Please note: all PROs are required to be administered prior to administration of study drug and prior to any other study assessment(s) to ensure the validity of the instruments is not compromised, and data quality meet requirements of regulatory authorities and best practices (FDA 2009; Fairclough 2010).

Participant-reported outcome data will be elicited from participants in this study to better characterize the clinical profile of ocrelizumab. These PRO measurements are described in Sections 5.14.1, 5.14.2, and 5.14.3. Please note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Due to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events.

Participants who are unable to complete exploratory assessments (e.g., ePROs) due to physical/disease limitations will not be excluded from the study.

5.14.1 Modified Fatigue Impact Scale

The MFIS will assess change in the level of fatigue during the double-blind, double-dummy treatment period. 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.

English version of MFIS is provided in Appendix 5.

5.14.2 The Center for Epidemiologic Studies Depression Scale

The CES-D will be used to evaluate participants for depressive symptoms during the double-blind, double-dummy treatment period. The CES-D is a 20-item self-report instrument that asks participants to rate their feelings and behaviors over the past week on a 4-point Likert scale, from "Rarely or none of the time (less than 1 day)" to "Most or all of the time (5–7 days)." Only a total scale score is calculated for the CES-D.

English version of CES-D is provided in Appendix 6.

5.14.3 The Short Form-36 Health Survey

The SF-36 Health Survey (version 2) is a generic quality of life instrument that has been widely tested for its psychometric properties and is widely used in clinical and epidemiological studies. The SF-36 contains 36 items and measures 8 health domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The SF-36 yields a score for each domain, as well as summary scores for the physical and mental dimensions. It can be completed in 5–10 minutes.

English version of the SF-36 Health Survey is provided in Appendix 7.

5.14.4 Participant's Assessment of Treatment Benefit

The Participant Perception of Treatment Questionnaire will be assessed after administration of PRO instruments at each visit in which PRO assessments are made, except for baseline. Specifically, participants will be asked whether they think their MS has become better, become worse or been stable since baseline. This question will serve as a global assessment from the participant perspective and will provide a useful anchor to help interpret the clinical meaningfulness of PRO results.

5.15 PHARMACOECONOMIC ASSESSMENTS/EQ-5D

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 and will be administered as per schedule of activities.

The EQ-5D (formerly known as EuroQoL) is a generic, preference-based health-related quality of life instrument. It has 5 dimensions assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 possible levels. Different combinations of responses are utility-weighted to produce a single health utility index. The Visual Analog Scale measures self-reported health on a scale between "worst imaginable" and "best imaginable" health states.

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.

5.16 OPTIONAL EXPLORATORY SUBSTUDIES

Participants who are randomized to the main Study WA21092 have the option to participate in exploratory substudies upon separate consent and fulfillment of additional exploratory substudy protocol criteria. The OCT Exploratory Substudy is included in the main study protocol (see Section 5.16.1 and Appendix 8). Other exploratory substudies are run under separate study protocols: substudy of brain and spinal cord MRI in participants with MS participating in Study BE29352 (OPERA); 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); and the assessment of ocrelizumab treatment effects on disability in participants with MS enrolled in the Phase III Orchestra program using multimodal evoked potentials and high-resolution electroencephalogram (EEG; Study BE29354). Substudies will be run only at the specifically assigned sites that are referred to in the substudy protocols.

5.16.1 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 9) and in the Imaging Review Charter.

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.

5.17 OPEN-LABEL EXTENSION PHASE

5.17.1 Open-Label Extension Phase Screening Period

Participants who have completed the 96-week, double-blind, double-dummy treatment period, and who, in the opinion of the Treating Investigator, may benefit from treatment with ocrelizumab, will be offered the opportunity to participate in the OLE phase of the study. Eligible participants who are not willing to participate in the OLE phase of the study will be entered into the safety follow-up period (see below).

It should be noted that in the case of a participant who initially declines participation in the OLE phase and subsequently reconsiders the decision, the participant will have up to 24 weeks after the Week 96 visit to enter the OLE phase. In this instance, he or she should not have taken any prohibited medication as specified in Section 5.5.2.1.

Participants who have consented to participate in the OLE phase will enter an OLE phase screening period to be evaluated for eligibility. The OLE phase screening period will start after all assessments at the Week 96 visit have been performed, and it should last up to 4 weeks. It is possible that the OLE phase screening period could be longer than 4 weeks. If a prolongation of the OLE phase screening period is needed, it should be discussed with the Sponsor on a case-by-case basis.

Information from assessments performed during the Week 96 visit will be used to verify the eligibility of the participant for the OLE phase of the study. Please see Section 5.4.

During the OLE phase screening period, all participants should receive Rebif/Rebif placebo (depending on initial arm assigned to) until the first infusion of Cycle 5. Please see Table 7 and Table 11 for more details regarding the Rebif/Rebif placebo dosing regimen.

Participants who withdraw from the OLE phase screening period will also be entered into the safety follow-up period (see below).

5.17.2 Open-Label Extension Phase

The OLE phase starts on the first infusion of Cycle 5 with continued dosing cycles every 24 weeks and up to the end of study (see Section 4.1.9). Participant treatment allocation during the double-blind, double-dummy treatment period will not be unblinded until the last data point from the last participant is received, as required for statistical analysis defined in Section 8.2 and the SAP (see Sections 4.1.8 and 6.4).

Study procedures at this visit will also include the following, but are not limited to:

- Physical examination
- Neurological exam
- Routine safety laboratory examinations (blood and urine sampling), HBV DNA (if applicable), FACS analysis, immunoglobulin levels

The first cycle of the OLE phase (Cycle 5) will consist of 2 IV infusions of 300 mg ocrelizumab separated by 14 days. Subsequent cycles (Cycles 6, 7, 8, etc.) will be with single IV infusions of 600 mg ocrelizumab to all participants enrolled in OLE phase of the study.

Note: This initial dual infusion is designed to both optimize the initial treatment effect and to minimize any IRRs for participants initially assigned to the ocrelizumab placebo/Rebif verum arm. In order to avoid unblinding of the assigned arm in the double-blind, double-dummy treatment period, both arms should receive dual infusion as described above.

Participants who are pregnant and breastfeeding should continue to follow 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.

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

Participants participating in OLE phase will be assessed at clinical visits every 24 weeks as per the schedule of activities (see Table 1). For the description of the assessments, please see Section 5.10.2.

The mechanisms necessary to guarantee assessor blindness are not necessary during the OLE phase. All required assessments during the OLE phase should occur as described in Section 1.3. It is recommended that the same EDSS assessor perform the test throughout the OLE phase.

Visits should be scheduled with reference to the date of first infusion during the OLE phase (Cycle 5). The visit for the second infusion should be scheduled 14 days after the first infusion of Cycle 5. A minimum interval of 20 weeks should be kept between the ocrelizumab second infusion of Cycle 5 and the next infusion at Cycle 6. A minimum of 22 weeks should occur between ocrelizumab single infusions administered during Cycle 6 onward. In the unforeseen cases that an infusion is delayed, additional tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted. At infusion visits, participants should remain in observation for at least 1 hour after the completion of the infusion.

In order to verify re-treatment criteria for infusions in Cycle 6 onwards, participants should attend a scheduled visit 2 weeks prior to the infusion visit.

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 should have an EDSS performed by the Examining Investigator, whenever possible within 7 days of the relapse onset date. Other tests/assessments may be done as appropriate.

Please see Section 7.3.5.1 for guidance on the diagnosis of PML.

5.17.3.1 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 3). 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.

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.

5.17.3.2 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 pre-planned, scheduled study visits. Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the participant.

Participants with new neurological symptoms suggestive of relapse should have an EDSS performed by the Examining Investigator, whenever possible within 7 days of the relapse onset date. Other tests/assessments may be done as appropriate. It should be noted if, during the OLE screening period, Rebif/Rebif placebo dose modification is necessary in the case of ALT elevations, then unscheduled visits may be required for dispensing of study medication (please see Section 6.2).

See Section 7.3.5.1 for guidance on the diagnosis of PML.

5.17.3.3 Withdrawal Visits in the Open-Label Extension Phase

At the moment a participant meets one 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 schedule of activities (Table 3) and should be entered into the safety follow-up period.

For participants who have withdrawn from 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 (i.e., 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 5.5.2.1 for recommendations on alternative treatments for MS). 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.

5.17.3.4 *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

During the double-blind, double-dummy treatment period, participants will be randomly assigned into 1 of 2 treatment groups:

- **Group A:** Ocrelizumab 600 mg dosing regimen (given as dual infusions of 300 mg of ocrelizumab 14 days apart for the first 24 weeks and single infusions of 600 mg every 24 weeks thereafter)
- **Group B:** Rebif SC injections, 3× weekly

Table 7 Treatment Groups and Schedule of Study Medication during the Double-Blind, Double-Dummy Treatment Period

Treatment Group	Schedule of Study Medication
Group A Ocrelizumab 600 mg regimen	Two IV infusions of ocrelizumab 300 mg separated by 14 days for the first 24 weeks, followed by single IV infusions of ocrelizumab 600 mg every 24 weeks thereafter AND Placebo Rebif subcutaneous injections, 3× weekly.
Group B Rebif	Rebif subcutaneous injections, 3× weekly AND Two IV infusions of placebo ocrelizumab 300 mg separated by 14 days for the first 24 weeks, followed by single IV infusions of placebo ocrelizumab 600 mg every 24 weeks thereafter.

The first IV infusion of ocrelizumab or placebo, or the first SC injection of Rebif or placebo will be administered on study Day 1.

During the OLE phase screening period, participants will continue to receive blinded treatment according to their initial assignment:

- **Group A:** Rebif placebo SC injections, 3× weekly
- **Group B:** Rebif SC injections, 3× weekly

During the OLE phase, all participants will receive ocrelizumab IV infusions every 24 weeks. At Cycle 5, participants will receive 2 infusions of 300 mg ocrelizumab IV separated by 14 days during the 24-week cycle. Beginning with Cycle 6, participants will receive ocrelizumab 600 mg every 24 weeks.

Please note: 100 mg of methylprednisolone IV will be administered prior to each IV infusion of ocrelizumab/ocrelizumab placebo during the double-blind, double-dummy treatment period and prior to each IV infusion of ocrelizumab during the OLE phase. In the event that the use of methylprednisolone is contraindicated for the participant, use of an equivalent dose of an alternative steroid is allowed as premedication.

6.1 OCRELIZUMAB

6.1.1 Preparation and Administration of Ocrelizumab Infusions

Detailed instructions for the preparation of the infusion bags containing the study drug will be provided separately in the Dose Preparation Guidelines.

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. Participants receiving ocrelizumab treatment will need to remain under observation at the clinic for at least 1 hour after the infusion. It is anticipated that the participant will need to stay at the hospital or clinical site for a full day for the infusion visit.

6.1.1.1 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 or ocrelizumab-matching placebo into an infusion bag containing 0.9% sodium chloride, to a final drug concentration of approximately 1.16 mg/mL. Specific instructions are provided separately in the Dose Preparation Guidelines. 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.

Prior to the start of the infusion, please ensure 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.

6.1.1.2 Infusion Procedures

Ocrelizumab 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.

All participants should receive pretreatment before the infusion (see Section 6.1.2).

6.1.1.3 Dual Infusion Cycle (Cycle 1 and Open-Label Phase Cycle 5)

The first cycle of the double-blind double-dummy treatment period (Cycle 1) and OLE phase (Cycle 5) will consist of 2 infusions of 300 mg ocrelizumab IV administered 14 days apart. For each infusion it is necessary to prepare a single infusion bag containing 300 mg ocrelizumab. Specific instructions will be provided separately in the Dose Preparation Guidelines and must be followed exactly. The infusion should be started at a rate of 32 mL/h. This should be escalated at the rates shown in Table 8.

Table 8 Infusions of Ocrelizumab 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).

6.1.1.4 Single Infusion Cycles (Cycles 2 - 4, and Open-Label Phase Cycle 6 Onwards)

Cycles 2–4 of the double-blind, double-dummy treatment period and Cycle 6 onwards in the OLE phase will consist of 1 infusion of 600 mg ocrelizumab IV 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/ocrelizumab placebo. Specific instructions will be provided separately in the Dose Preparation Guidelines and must be followed exactly. The infusion should be started at a rate of 40 mL/hr. This should be escalated at the rates shown in Table 9.

Table 9 Subsequent Infusions 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.

6.1.1.5 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 10.

Table 10 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 the 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 of this protocol and to the current version of the Ocrelizumab IB for further details on the alternative shorter infusion option, including safety information.

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

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour in order to be able to administer 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 for up to 24 hours at 2–8°C. The 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).

As noted above, the diluted infusion bags should be at room temperature prior to administration to the participant.

6.1.2 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 premedication (Emery et al. 2006). A recent integrated analysis of participants with MS treated with ocrelizumab revealed that the addition of antihistamines to pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold (OCREVUS USPI).

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 an equivalent dose of an alternative). 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 event that the use of methylprednisolone is contraindicated, use of an equivalent dose of alternative steroid should be used as premedication prior to the infusion. Participants administered a sedating antihistamine medication for the treatment or prevention of infusion reactions should be given appropriate warnings concerning drowsiness and potential impairment of the ability to drive or operate machinery.

It is also recommended that the infusion be accompanied by prophylactic treatment with an analgesic/antipyretic such as 1 g acetaminophen/paracetamol 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 1 g acetaminophen/paracetamol, and IM or slow IV antihistamine administration, such as diphenhydramine (25–100 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 associated respiratory symptoms (stridor, wheeze or bronchospasm), additional treatment with bronchodilators may be indicated.

One participant with well-controlled asthma at baseline experienced an acute asthma attack following their first rituximab infusion. Physicians should; therefore, monitor participants with a history of asthma carefully and institute an appropriate treatment if signs and symptoms of asthma are noticed.

After completion of the infusion, the IV cannula should remain in situ for at least 1 hour in order to be able to administer 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.

Section 6.1.3 details the reduction, interruption or discontinuation of the infusion in the event of an infusion reaction.

6.1.3 Ocrelizumab Dose Modifications, Interruptions, and Delays

No ocrelizumab 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 participants, ocrelizumab treatment may need to be discontinued. Guidance is provided below.

6.1.3.1 Handling Infusion 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 (CTCAE Grade 1 or 2; Appendix 3) 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 50–25 mL/hr or from 100–50 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 an infusion-related event (CTCAE Grade 3) or flushing, fever and throat pain cluster 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.

Please note: 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 should be withdrawn from treatment and should enter the safety follow-up period.

6.1.4 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 reaction, 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.

Please note: any critical blinded laboratory values for IgG, ANC, and CD4 will be provided to the Principal 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.

6.2 REBIF

6.2.1 Dose and Schedule of Rebif

See Table 11 for overview of Rebif dosing regimen.

The first SC injection of Rebif/placebo will be administered on study Day 1. Participants will be instructed by a nurse or investigator how to self-administer the injections; the first dose of Rebif/placebo will be self-administered under the supervision of a nurse or physician. Thereafter, participants will self-administer their Rebif/placebo treatment 3 times weekly. Rebif/placebo must be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same 3 days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart. Participants must be

instructed in the use of aseptic techniques when administering Rebif/placebo injections. Participant understanding and use of aseptic self-injection techniques and procedures must be periodically re-evaluated.

Since Rebif needs to be stored at 2–8°C, it is recommended to remove the syringe from refrigerator at least 30 minutes prior to use. Participant should be reminded not to heat or microwave a syringe.

When starting treatment with Rebif, the dose will be gradually escalated (Table 11). The Rebif/placebo initiation package corresponds to the participant needs for the first month of treatment.

Table 11 Overview of Rebif Dosing Regimen

	Treatment Initiation		Treatment Continuation	Dose modification (if required)
Week	Weeks 1–2	Weeks 3–4	Week 5 onwards	–
Study Day	1–14	15–28	29 +	At any time Day>29
Dose of Rebif	Rebif 8.8 µg (1 pre-filled syringe [0.2 mL] containing 2.4 MIU of IFN β-1a) SC 3 × per week	Rebif 22 µg (1 pre-filled syringe [0.5 mL] containing 6 MIU of IFN β-1a) SC 3 × per week	Rebif 44 µg (1 pre-filled syringe [0.5 mL] containing 12 MIU of IFN β-1a) SC 3 × per week	Rebif 22 µg (1 pre-filled syringe [0.5 mL] containing 6 MIU of IFN β-1a) SC 3 × per week

Note: Rebif is provided in a blinded fashion.

Nonsteroidal anti-inflammatory drugs (ibuprofen) or acetaminophen are recommended in case of injection site reaction; the investigator should follow the local label for further information.

Note: During the OLE phase screening period, administration of Rebif/Rebif placebo SC 3× per week should occur. If during this period, the participant decides not to participate in the OLE phase then administration of Rebif/Rebif placebo 3× per week should be terminated.

6.2.2 Rebif Dose Modifications, Interruptions, and Delays

Rebif/Rebif placebo should be taken 3× a week. Rebif/Rebif placebo should never be taken on 2 consecutive days. If a participant misses a dose, then the next dose must be taken as soon as possible. The participant should avoid taking Rebif/Rebif placebo on the following day. The participant should return to their regular schedule the following week. If a participant takes more than the prescribed dose or takes it on 2 consecutive days, they should inform the investigator immediately.

The Rebif/Rebif placebo dosage can be modified at the discretion of the Principal Investigator due to safety reasons at any time; the Principal Investigator should follow information on the local label for further information.

Asymptomatic increases in laboratory parameters of hepatic function have been associated with Rebif.

In case of elevation of liver function tests the following rules will apply:

ALT ≥ 10 × ULN OR jaundice or other clinical symptoms of liver dysfunction	In case of detection of elevated **ALT ≥ 10 × ULN**, jaundice or other clinical symptoms of liver dysfunction the injections of Rebif/Rebif placebo must be discontinued permanently. The monitoring of liver function tests should be continued on a monthly basis until return to normal baseline levels or NCI CTCAE v4.0 Grade 1 toxicity (ALT: > ULN – 3.0 × ULN). A consultation with hepatologist is recommended. Participants should move to safety follow-up period.
ALT ≥ 5 × ULN	In case of detection of elevated **ALT ≥ 5 × ULN** (but below 10 × ULN) the injections of Rebif/Rebif placebo must be discontinued temporarily. Additional blood chemistry panel including AST, ALP, GGT, and bilirubin should be performed biweekly until no further increase is observed. Subsequently, ALT analysis has to be performed every month until return to normal baseline levels or NCI CTCAE v4.0 Grade 1 toxicity (ALT: > ULN – 3.0 × ULN). A consultation with hepatologist should be considered as per investigator judgment. If causes of toxicity other than possible treatment with Rebif are excluded, the participant may then be cautiously re-challenged with Rebif/Rebif placebo 22 µg provided in a blinded fashion upon request to IxRS. The monitoring of liver function tests should continue on a monthly basis. If there is no further recurrence of toxicity, participant may continue treatment with Rebif/Rebif placebo 44 µg provided in a blinded fashion upon investigator's request to IxRS. **In case of recurrence of toxicity (ALT > 3 × ULN, or other clinical symptoms of liver dysfunction) the injections of Rebif/Rebif placebo should be discontinued permanently.** Participants should move to safety follow-up period. Please note: Re-initiation of therapy with Rebif following elevation of liver function tests can only be considered once.
ALT > 3 × ULN	In case of detection of elevated **ALT > 3 × ULN** (but below 5 × ULN) additional blood chemistry panel including AST, ALP, GGT and bilirubin should be performed biweekly until no further increase is observed. Subsequently, ALT analysis has to be performed every month until return to normal baseline levels or NCI CTCAE v4.0 Grade 1 toxicity (ALT: > ULN – 3.0 × ULN).

6.3 FORMULATION, PACKAGING, AND LABELING

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

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

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

6.3.1 Ocrelizumab

6.3.1.1 Formulation

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 dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15 cc Type I USP glass vial, fitted with a 20 mm fluoro-resin laminated stopper and an aluminum seal with a flip-off plastic cap. The vial contains 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. 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 0.2 μm or less).

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.

6.3.1.2 Packaging

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

For the double-blind treatment in Cycle 1, consisting of two 300 mg infusions 14 days apart, the study medication kit will contain 2 single-use liquid vials with ocrelizumab (or ocrelizumab placebo).

For each of the subsequent Cycles 2–4, consisting of a single 600 mg infusion, 2 kits will be dispensed. Each kit will contain 2 single-use liquid vials with ocrelizumab (or ocrelizumab placebo), from which only 3 vials should be used.

For the OLE phase, each study medication kit will contain 1 single-use vial. For OLE phase Cycle 5, consisting of two 300 mg infusions 14 days apart, 2 study medication kits will be supplied per infusion. For OLE phase Cycle 6 and each of the subsequent cycles consisting of 600 mg infusions, 2 study medication kits (of 300 mg ocrelizumab each) will be dispensed. Detailed instructions are provided separately in the Dose Preparation Guidelines.

6.3.1.3 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.

6.3.2 Rebif

6.3.2.1 Formulation and Packaging

Rebif (IFN β-1a) will be supplied as a liquid formulation for injection in pre-filled syringes.

The liquid formulation is supplied in syringes containing 0.2 mL or 0.5 mL of solution. These commercially available syringes will be provided to the sites by the Sponsor and re-labeled as investigational medicinal product.

The placebo to Rebif is provided as a liquid formulation in a pre-filled syringe containing 0.2 mL or 0.5 mL of 0.9% sodium chloride solution without any active substance.

The study medication kits, which will be used for the initial 4 weeks of treatment, will contain 12 pre-filled syringes, either 6 × 8.8 μg and 6 × 22 μg OR placebo. The study medication kits that will be used for treatment continuation will contain 12 pre-filled syringes 12 × 44 μg of IFN β-1a or 12 × 22 μg of IFN β-1a or placebo.

The Rebif and Rebif placebo pre-filled syringes are for SC use only.

Please note: if Rebif dose modification is required due to laboratory abnormalities possibly related to the treatment with Rebif, the investigator (the treating physician) will need to notify IxRS and the blinded study medication (Rebif placebo or Rebif verum) will be dispensed accordingly. In addition, to ensure participant safety in the study, unscheduled visits may be required for additional assessments, monitoring and for dispensing study medication.

The study medication labels will be produced in accordance with the local requirements. The strength will be presented as follows: 44 μg/22 μg/placebo.

6.3.2.2 Storage of Rebif

Rebif/Rebif placebo pre-filled syringes need to be stored in a refrigerator at 2–8°C, in the original package in order to protect from light. The participant may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.4 BLINDING AND UNBLINDING

During the double-blind phase of the study, the Participant Randomization List will be generated by IxRS with use of a pre-defined randomization specification.
The Randomization List will not be available at the study center, to the Roche monitors, project statisticians or to the Sponsor's project team. Unblinding of treatment assignment should not occur except in the case of emergency situations, where the knowledge of what study medication the participant is receiving is critical for clinical management. Principal Investigators are asked to contact the Roche Medical Monitor, prior to unblinding any participant, in order to discuss the medical necessity for unblinding. Any request from the investigator for information about the treatment administered to study participants for another purpose must be discussed with Roche. Unblinding will be performed by means of an IxRS. As per regulatory reporting requirements, Roche will unblind the identity of the study medication for serious adverse events that are considered by the investigator or the Sponsor to be related to study drug, that are unexpected as per safety reference document(s), e.g., IB, Core Data Sheet, and Summary of Product Characteristics, and that are not exempted from unblinding as per Section 7.2.2.2. Details of participants who are unblinded during the study will be included in the Clinical Study Report.

In the double-blind phase of the study, unblinding for analysis of biological samples, PK data analysis, or ongoing safety monitoring by a Data Monitoring Committee (DMC), will be performed according to procedures in place to ensure integrity of the data.

Participant treatment allocation during the double-blind, double-dummy treatment period will not be unblinded until the last data point from the last participant is received, as required for statistical analysis defined in Section 8.2 and the SAP (see Section 4.1.8).

6.5 ACCOUNTABILITY OF INVESTIGATIONAL MEDICINAL PRODUCT AND ASSESSMENT OF COMPLIANCE

6.5.1 Accountability of Investigational Medicinal Product

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

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

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

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) and quantity of the study medication dispensed to the participant
- The date(s) and quantity of the study medication returned by the participant

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

6.5.2 Assessment of Compliance

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

The study pharmacist should keep all ocrelizumab/ocrelizumab placebo vials to measure compliance. All participants will be asked to return on regular intervals all used and unused Rebif/Rebif placebo containers to the site as a measure of compliance.

6.6 DESTRUCTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT/COMPARATOR

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

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 eCRF "MS relapse" eForm.

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

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 investigators review and, if warranted, update participant's immunizations in accordance with country medical immunization guidelines (see Section 5.5.3).

7.1.1.1 Intensity of Clinical Adverse Events

Adverse events will be graded according to CTCAE, v4 and is provided to the investigator in a separate handout entitled "Common Terminology Criteria for Adverse Events v4.0"- see Appendix 3.

Adverse events not listed by the CTCAE and IRRs as a comprehensive entity 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 in Section 7.1.1.3, should be reported as an serious adverse event.

7.1.1.2 Drug–Adverse Event Relationship

Relationship of the adverse event to the treatment should always be assessed by the investigator. The causality relationship of study drug to the adverse event will be assessed by the investigator as either: Yes or No. See Appendix 1 for more details.

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**; please 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 (please 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-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

The following are not considered as a 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 Concomitant Procedures/Treatments eCRF.
- Hospitalization to receive trial medication such as infusions of ocrelizumab unless this is prolonged (more than 24 hours)
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone (or with another equivalent corticosteroid; see Section 5.5.2)

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 ADRs that are considered expected, refer to the current version of the Ocrelizumab IB.

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 2).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 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 appear on electronically produced laboratory reports submitted directly from the central laboratory.

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 eForm in the 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 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 pharmacodynamic effect and is not an adverse event.

During the double-blind, dummy-dummy treatment period, blinded laboratory values for IgG, ANC and CD4 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 (see Section 6.1.4) and these laboratory values have normalized. During the OLE phase from Cycle 6 onward, these laboratory values will not be blinded.

7.1.3.2 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 7.1.1.2 and Section 7.1.1.3).

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 page and the Medical Monitor should be informed.

7.2.2 Reporting of Serious Adverse Events

7.2.2.1 Immediate Reporting to the Sponsor

Any clinical adverse event or abnormal laboratory test value that is serious (as defined in Section 7.1.1.3), or adverse events of special interest (as defined in Section 7.1.1.4), which occur 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.

After the participant signs the Informed Consent Form, but prior to initiation of study medication, only serious adverse events caused by a protocol-mandated intervention will be collected (e.g., serious adverse events related to MRI examination). After first dose of study medication, all serious adverse events must be reported.

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. 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 a 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.

A death occurring during the study or information related to such occurrence that comes to the attention of the investigator during the study must be reported immediately to the Sponsor, whether considered treatment-related or not.

Of specific importance is the prompt reporting of serious infections. In particular, PML should be reported as a 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 (see Appendix 2).

7.2.2.2 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/
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 Ocrelizumab IB and the E.U. Summary of Product Characteristics for IFN β-1a.

In principle, adverse events which 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.
This requires unblinding of participant treatment allocation. Investigators, IRBs, and ECs will receive blinded reports unless local regulations require that unblinded expedited reports are sent.

In the double-blind phase of this study, the relation to study medication for certain types of adverse events cannot be assessed based on single case evaluation. Therefore, in

order to prevent unnecessary unblinding of study participants during the double-blind phase of the study, the following events are exempted from expedited reporting:

- Neoplasms benign, malignant, and unspecified (including cysts and polyps)
- Infections and infestations with the exception of opportunistic infections (including PML and reactivation of viral infections)

The DMC will review adverse events at periodic meetings and assess their relation to study medication based on review of aggregate unblinded safety information until the primary analysis is performed. Following unblinding after the 96-week period, independent Data Monitoring Committee (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 during this study. 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 IB. 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 immunoglobulins are found in breast milk.

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 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 end of pregnancy and breastfeeding.

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

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 see the current version of the Ocrelizumab IB.

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 an infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to, pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia. Some of these events have been severe enough to warrant interruption or discontinuation of the infusion. Symptoms are often reversible if the infusion is interrupted and/or participants receive additional treatment with an antihistaminic, acetaminophen, epinephrine or an IV corticosteroid.
See Sections 6.1.2 and 6.1.3 for further information.

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 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 IB.

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

In interventional clinical studies, there were no reports of hepatitis B reactivation in participants with MS treated with ocrelizumab, but it had been reported for 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 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 Section 7.3.1.2.

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: 27–175weeks).

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 with 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.

Impaired Response to Vaccination

The degree of impairment of B cell–dependent humoral response to neo-antigens and polysaccharide antigens and its clinical relevance are currently unknown in participants with MS.

After treatment with ocrelizumab over 2 years in pivotal clinical trials, the proportion of participants 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-positive 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 increase 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 7.3.5. Please see the current version of the Ocrelizumab IB for more details regarding PML risk and see Section 7.3.5.1 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 Inge-mediated hypersensitivity to ocrelizumab must not be treated.

7.3.2 Rebif

Participants should be informed of the risks associated with taking Rebif. The most frequent Rebif adverse reactions of which the participants should be made aware have been summarized in Section 2.1.5.

Depression and suicide ideation are known to occur in increased frequency in the MS and in association with IFN use. Therefore, all participants should be advised to immediately report any symptoms of depression and/or suicidal ideation to investigator. Participants exhibiting depression should be monitored closely and treated appropriately. Cessation of double-blind treatment should be considered.

Injection site necrosis has been reported in participants using Rebif. To minimize the risk of injection site necrosis participants should be advised to:

- Use an aseptic injection technique
- Rotate the injection sites with each dose

If the participant experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the participant should be advised to consult with their physician before continuing injections with Rebif/Rebif placebo. If the participant has multiple lesions, injections should be discontinued until healing has occurred. Participants with single lesions may continue provided that the necrosis is not too extensive.

Rebif, like other IFN β, has a potential for causing severe liver injury including acute hepatic failure. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified. Please see Section 6.2.2 for additional guidelines.

7.3.3 Corticosteroids

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

7.3.4 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. See the local prescribing information.

7.3.5 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 viruria 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 and/or progressive 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 7.3.5.1 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 enter the safety follow-up phase of 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 version of the Ocrelizumab IB.

7.3.5.1 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

The following diagnostic algorithm framework (Figure 2) will be implemented in this study.

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 4). 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 2).

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 two conditions (see Table 12)
- 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 2) 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, an additional plasma, urine, as well as a CSF sample should be obtained for JCV analysis. Cerebrospinal fluid samples will be analyzed upon receipt with high-sensitivity test 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. For details, please refer to the most up-to-date Laboratory Manual providing storage conditions and shipment instructions.

MRI Assessment

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and

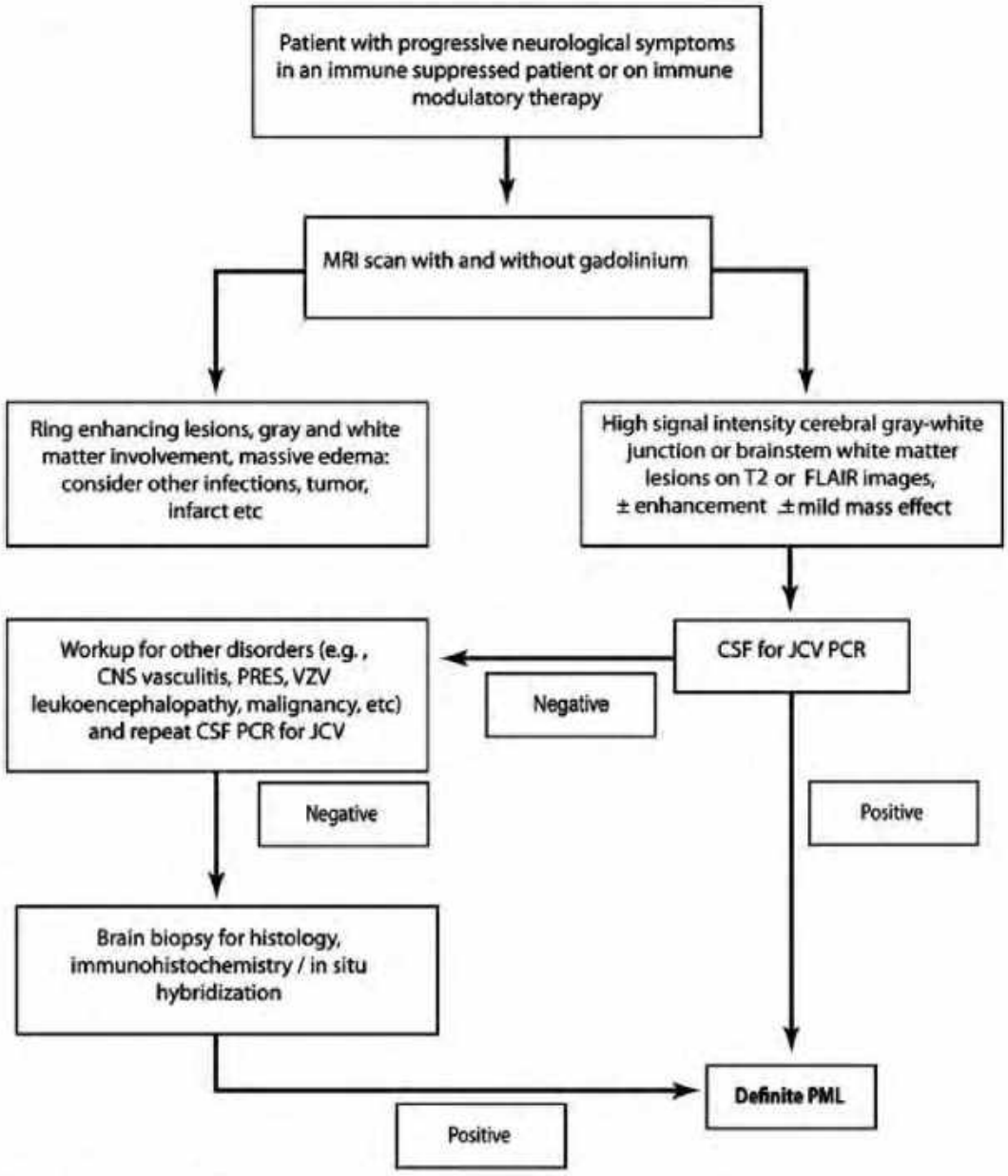
T2-weighted and T1-weighted sequences, with and without Gd, should be performed to assess participants with neurological changes suggestive of PML (Figure 2)

- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 13 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 2 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 12 Clinical Features to Distinguish between MS Relapse 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 13 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 13 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 for the double-blind portion of the study were specified in a separate SAP which was finalized prior to the interim database lock and unblinding of the study database. A separate SAP for the OLE will be finalized prior to the final study database lock.

8.1 STUDY ENDPOINTS

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is annualized protocol-defined relapse rate by 2 years (96 weeks).

Protocol-defined relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS. Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications) and immediately preceded by a stable or improving neurological state for least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least half a step on the EDSS scale, or 2 points on one of the appropriate 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. Please note: Sexual dysfunction and Fatigue will not be scored.

Adjudication of protocol-defined relapses will be performed by the Sponsor based on pre-specified criteria, applied to data collected by investigator, in a blinded fashion.

8.1.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- The time to onset of confirmed disability progression for at least 12 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period (see Section 5.10.2.2 for the definition of confirmed disability progression)
- The total number of T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96
- The total number of new, and/or enlarging T2 hyperintense lesions as detected by brain MRI at Weeks 24, 48, and 96
- The proportion of participants who have confirmed disability improvement for at least 12 weeks, with the initial event of neurological improvement occurring during the 96-week double-blind, double-dummy treatment period
- The time to onset of confirmed disability progression for at least 24 weeks with the initial event of neurological worsening occurring during the 96-week, double-blind, double-dummy, treatment period (see Section 5.10.2.2 for the definition of confirmed disability progression)
- The total number of new T1-hypointense lesions (chronic black holes) at Weeks 24, 48, and 96
- The change in MSFCS score from baseline to Week 96

- The percentage change in brain volume as detected by brain MRI from Week 24 to Week 96
- The change in SF-36 PCS Score from baseline to Week 96
- The proportion of participants who have NEDA by Week 96

8.1.3 Exploratory Efficacy Endpoints

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

- The change in low-contrast visual acuity from baseline to Weeks 48 and 96
- The change in the SDMT from baseline to Weeks 48 and 96
- The proportion of relapse-free participants by 96 weeks
- The change in total T2 hyperintense lesion volume as detected by brain MRI from baseline to Week 96
- The ARR, based on all clinical at the end of the 96-week comparative treatment period (protocol-defined relapses are a subset of all clinical relapses)
- The ARR of relapses requiring IV steroid therapy
- The ARR of severe relapses
- The percentage change in brain volume as detected by brain MRI from baseline to Week 96
- The change in MSFCS score from baseline to Week 48
- The cumulative change in EDSS scores, measured in AUC by Week 96
- The change in EDSS from baseline to Week 96
- The change in Timed 25-Foot Walk from baseline to Week 96
- The change in 9-HPT from baseline to Week 96
- The change in PASAT from baseline to Weeks 48 and 96
- The time to onset of sustained 20% increase in 9-HPT for at least 12 weeks
- The time to onset of sustained 20% increase in T25FWT for at least 12 weeks
- The change in fatigue, as measured by the MFIS total score from baseline to Week 96
- The change from baseline in participant-reported depressive symptoms, as measured by the CES-D, from baseline to Week 96
- Analyses of EQ-5D, collected at baseline, Week 48, and Week 96
- The change in Karnofsky Performance Status Scale from baseline to Week 96
- The percentage change in cortical grey-matter volume from baseline to Week 96
- The percentage change in white matter volume from baseline to Week 96
- The proportion of participants who have disability improvement confirmed for at least 24 weeks, with the initial event of neurological improvement occurring during the 96-week double-blind, double-dummy treatment period

- The proportion of participants who have disability improvement sustained for at least 12 weeks and sustained until the end of the 96-week, double-blind, double-dummy treatment period, with the initial event of neurological improvement occurring during the 96-week, double-blind, double-dummy treatment period
- The duration of the confirmed disability improvement
- The proportion of participants who at Week 96 have improved, stable or worsened disability, compared with baseline
- The change in Quality of Life, as measured by the SF-36 version 2 MCS Score from baseline to Week 96
- 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
- To evaluate the long-term safety of ocrelizumab treatment during the OLE phase of the study
- To evaluate the effects of switching from Rebif to ocrelizumab treatment

8.1.4 Safety

Safety will be assessed through regular neurological 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
- C-SSRS
- Standard hematology, chemistry, and urinalysis assessments
- Circulating B cell total and subsets, T cells, natural killer cells and other leukocytes
- Plasma immunoglobulins
- 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 *Streptococcus pneumoniae*
- MS relapses classified as serious
- Serial pregnancy tests (serum/urine β-hCG) will be performed in women of childbearing potential
- JCV plasma/urine sampling 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.

After the Week 96 visit of the last participant randomized, approximately 12 weeks may be needed to allow the confirmation of the last event of the 12-week confirmed disability progression. Therefore, the clinical cutoff date will occur approximately 12 weeks after

the last participant's Week 96 visit when the status is clarified for each participant. Database lock and unblinding of the Sponsor will occur several weeks after the clinical cutoff in order to clarify all outstanding queries. The sites and EDSS raters will remain blinded until approximately 24 weeks after the Week 96 visit of the last participant randomized to allow the confirmation of the last 24-week confirmed disability progression event, in case an updated analysis of this endpoint is requested at a later point.

The time to onset of confirmed disability progression for at least 12 weeks during the 96-week comparative treatment period, the proportion of participants who have confirmed disability improvement for at least 12 weeks with the initial event of neurological improvement occurring during the 96-week double-blind, double-dummy treatment period, and the time to onset of confirmed disability progression for at least 24 weeks during the 96-week comparative treatment period will be analyzed with use of pooled data across the 2 identical studies running as a part of the Phase III program, with respect to ocrelizumab group versus Rebif group.

All eligible participants will be randomized to treatment stratified by region (United States vs. ROW) and baseline EDSS (<4.0 vs. ≥ 4.0). All analyses will also be stratified by region (United States vs. ROW) and baseline EDSS (<4.0 vs. ≥ 4.0).

Some efficacy analyses will be undertaken for some subgroups, as agreed with regulatory authorities. Details of these subgroup analyses are presented in the SAP.

All analyses, summaries and listings will be performed with use of SAS® software (Version 9.2 or higher in a UNIX environment).

8.2.1 Primary Efficacy Analysis

The primary efficacy analysis for this trial will compare annualized protocol-defined relapse rate by 96 weeks between ocrelizumab group and Rebif group. The annualized relapse rates by 96 weeks will be analyzed with use of a negative binomial model, adjusting for region (United States vs. ROW) and baseline EDSS (<4.0 vs. ≥ 4.0). The adjusted ARR and the 2-sided 95% CIs for the relapse rates will be presented along with the p-value.

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

8.2.2 Secondary Efficacy Analyses

The statistical testing strategy for all secondary efficacy endpoints, the testing hierarchy and the rationale for this hierarchical order of secondary endpoints is fully explained in the SAP.

Secondary efficacy endpoints will be tested in hierarchal order, all at $\alpha = 0.05$ level. The first secondary efficacy endpoint will be tested if and only if the primary endpoint has

reached the significant level at 0.05 (e.g., P-value ≤0.05). With the exception of the 3 secondary efficacy endpoints, which will be analyzed at the pooled level (see Section 8.2), all secondary efficacy endpoints will be tested if and only if the secondary endpoint listed ahead of it has reached the significance level at 0.05.

Additional pooled analyses are also described in a separate SAP (called the pooled SAP). This document describes solely those analyses that will be performed on the 2 studies combined.

8.2.2.1 The Time to Onset of Confirmed Disability Progression for at Least 12 Weeks During the 96-Week Comparative Treatment Period

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 ≥84 days after the initial disability progression. Disability progression is defined as an increase of ≥1.0 point from baseline EDSS, if the baseline EDSS is between 0 and 5.5 points (inclusive), or an increase of ≥0.5 points, if the baseline EDSS is >5.5 points. Please note that the inclusion criterion of EDSS (0–5.5) only applies to screening EDSS. It is still possible that a participant's baseline EDSS (derived based on both screening and day 1 EDSS results) is >5.5. 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. All initial disability progression events up to Week 96 with corresponding confirmation visits at the next scheduled visit (see schedule of activities in Section 1.3) will be taken into account for the statistical analysis irrespective of whether or not the confirmation visit occurred during the treatment phase or after study drug discontinuation, or during the OLE phase. Thus, participants who prematurely discontinue study drug treatment should be kept in the study, and every effort should be made to follow-up their EDSS status at the next scheduled visit. Participants who according to the above definition did not have confirmed disability progression by Week 96 visit, time of early discontinuation of treatment, or loss to follow-up will be censored at the date of their last EDSS assessment.

Data from the 2 studies with respect to ocrelizumab group vs Rebif group will be pooled for analysis of this endpoint. To assess the validity of pooling data across the 2 RMS studies, demographic and baseline characteristics will be compared by trials.
The treatment effect (hazard ratio and CI) for confirmed disability progression within each trial will be compared between the 2 trials. In interpreting the trial comparisons with a view toward assessing the validity of the pooled dataset, the primary interest is in confirming that the treatment effect is qualitatively similar across the 2 studies – positive treatment effects (the estimated hazard to have confirmed disability progression in participants treated with ocrelizumab is numerically smaller than that in participants treated with Rebif) are shown in both studies. If the results from the 2 studies are not qualitatively similar (e.g., positive treatment effect is only shown in one study), data will

not be pooled. Further details regarding the assessment of poolability are provided in the SAP.

Time to confirmed disability progression for ocrelizumab group and Rebif group (across the studies) will be compared with use of a 2-sided log-rank test stratifying by region (United States vs. ROW), baseline EDSS (<4.0 vs. ≥4.0). 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. More details are provided in the SAP for the study.

8.2.2.2 Total Number of T1 Gadolinium-Enhanced Lesions as Detected by Brain Magnetic Resonance Imaging at Weeks 24, 48, and 96

The total number of T1 Gd-enhanced lesions will be calculated as the sum of the individual number of T1 Gd-enhanced lesions at Weeks 24, 48 and 96. Data from other unscheduled assessments will not be included in this summary or analysis.

A negative binomial model will be used to compare the difference between ocrelizumab and Rebif groups.

8.2.2.3 The Total Number of New and/or Enlarging T2 Hyperintense Lesions as Detected by Brain Magnetic Resonance Imaging at Weeks 24, 48, and 96

The same approach will be used for the statistical analysis as for the total number of T1 Gd-enhanced lesions.

8.2.2.4 Proportion of Participants who have Disability Improvement Confirmed for at Least 12 Weeks

This endpoint will be analyzed only for the subgroup of participants with a baseline EDSS score ≥ 2.0. Exactly the same approach to data derivation will be used for disability improvement as for disability progression (see Section 8.2.2.1, although note that, here, the endpoint is a binary improved/not improved variable, rather than a time-to-event endpoint). In particular, the same approach to the timing of the confirmation of disability improvement will be applied as for disability progression. The baseline EDSS score is the average of the EDSS score at the screening period and the EDSS score at the baseline visit, without rounding. For participants with a baseline EDSS score ≥2 and ≤5.5, disability improvement is defined as a reduction in EDSS score ≥ 1.0 compared with baseline EDSS score. For participants with a baseline EDSS score >5.5, disability improvement is defined as a reduction in EDSS score of 0.5. All participants without disability improvement will be counted as not improved, independent of follow-up time.

Data from the 2 studies with respect to ocrelizumab group vs. Rebif group will be pooled for analysis of this endpoint.

The proportions in treatment groups will be compared with use of the Cochran-Mantel-Haenszel (CMH) χ^2 test stratified by geographical region (United States vs. ROW) and baseline EDSS score (<4.0 vs. ≥ 4.0).

8.2.2.5 The Time to Onset of Confirmed Disability Progression for at Least 24 Weeks During the 96-Week Comparative Treatment Period

Time to confirmed disability progression between ocrelizumab group and Rebif group with use of a 24-week confirmation window for disability progression will be compared with use of the same analysis method for time to confirmed disability progression using a 12-week confirmation window. Time to confirmed disability progression (24-week confirmation) is defined as the time from baseline (Day 1) to the first disability progression, which is confirmed at the next regularly scheduled visit ≥ 161 days after the initial disability progression. All initial disability progression events up to Week 96 with corresponding confirmation visits at the next schedule visit (see schedule of activities in Section 1.3) will be taken into account for the statistical analysis. The same analysis principles as described in Section 8.2.2.1 will be applied to the 24-week disability endpoint.

Data from the 2 studies with respect to ocrelizumab group versus Rebif group will be pooled for analysis of this endpoint.

8.2.2.6 Total Number of New T1-Hypointense Lesions (Chronic Black Holes) at Weeks 24, 48, and 96

The same approach will be used for the statistical analysis as for the total number of T1 Gd-enhanced lesions.

8.2.2.7 The Change in MSFCS Score from Baseline to Week 96

The change in MSFCS from baseline to Week 96 will be compared between ocrelizumab group and Rebif group with use of a Mixed-Effect Model Repeated Measures (MMRM) analysis, adjusting for baseline MSFCS, region (United States vs. ROW), and baseline EDSS (<4.0 vs. ≥ 4.0).

8.2.2.8 The Percentage Change in Brain Volume as Detected by Brain Magnetic Resonance Imaging Scan from Week 24 to Week 96

The change in brain volume as detected by brain MRI from week 24 to Week 96 will be compared between ocrelizumab group and Rebif group with use of an MMRM analysis. Baseline covariates here will be as follows: brain volume at Week 24, baseline Gd lesion (present or not), region (United States vs. ROW), and baseline EDSS score (<4.0 vs. ≥ 4.0).

8.2.2.9 Change in Quality of Life as Measured by the Short Form-36 Version 2 Physical Component Summary Score from Baseline to Week 96

The change in quality of life, as measured by the SF-36 PCS score from baseline to Week 96 will be compared between ocrelizumab group and Rebif group with use of a MMRM analysis. Baseline covariates here will be as follows: baseline PCS score, region (United States vs. ROW), and baseline EDSS (<4.0 vs. ≥ 4.0).

8.2.2.10 Proportion of Participants Who Have No Evidence of Disease Activity by Week 96

This endpoint will be defined only for those participants with a baseline EDSS score ≥ 2.0. All available data during the 96-week treatment period will be used for the analysis. Participants who complete the 96-week treatment period will be considered as having evidence of disease activity if at least one protocol-defined relapse, a confirmed disability progression (CDP) event having occurred or at least one MRI scan showing MRI activity (defined as Gd-enhancing T1 lesions, or new or enlarging T2 lesions) was reported during the 96-week treatment period, otherwise the participant will be considered as having NEDA. Participants who discontinue treatment early with at least one event before early discontinuation will be considered as having evidence of disease activity.

Even if an event was not reported before early discontinuation, the participant will be considered as having evidence of disease activity if the reason for early discontinuation is lack of efficacy or death; otherwise, it will be considered a missing observation.

The proportions within treatment groups will be compared with use of the CMH χ^2 test stratified by region (United States vs. ROW) and baseline EDSS (<4.0 vs. ≥ 4.0).

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 for this study has been estimated based on data from previous RRMS trials, with the use of 2-sided tests with an experiment-wise $\alpha = 0.05$. The ARR among participants receiving ocrelizumab at 96 weeks is predicted to be 0.165 (standard deviation of approximately 0.60), as compared with 0.33 (standard deviation of approximately 0.80) among participants receiving the control treatment, Rebif (this represents a RR of 50% on ocrelizumab compared with the active comparator). For the ARR, a t-test has been used to determine the sample size between ocrelizumab and the control arm. The sample size of 400 participants per arm provides 84% power, maintaining the type I error rate of 0.05, and assuming a dropout rate of 20% approximately (assuming RR among participant dropout is 25%).

For confirmed disability progression, a 2-group test of equal exponential survival with exponential dropout is used to determine the sample size. Assuming the 2-year confirmed disability progression rate is 18% for the Rebif arm and 12.6% for the ocrelizumab arm (this represents a RR of 30% on ocrelizumab compared with the active comparator), and assuming a dropout rate of 20 percent over 2 years approximately, the sample size of 400 participants arm will provide 80% power, maintaining the type I error rate of 0.05 based on the pooled analysis of 2 RMS trials (800 participants treated with ocrelizumab 600 mg and 800 participants treated with Rebif).

8.2.5 Hypothesis Testing

The hypotheses to be tested are:

- H_0 (null hypothesis): there is no statistically significant difference in annualized protocol-defined relapse rate at 2 years between ocrelizumab group and Rebif group
- H_1 (alternative hypothesis): there is a statistically significant difference in protocol-defined ARR at 2 years between ocrelizumab group and Rebif group

Protocol-defined ARR at 2 years between the ocrelizumab group and Rebif group will be compared with use of a negative binomial model adjusting region (United States vs. ROW) and baseline EDSS (<4.0 vs. ≥ 4.0). If the test result for comparing 600 mg ocrelizumab and Rebif groups is statistically significant at $\alpha < 0.05$ level (2-sided test), we will conclude that the 600 mg ocrelizumab group demonstrated a superior effect of reducing protocol-defined ARR, when compared with the Rebif group.

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 2 populations for the efficacy analysis. All efficacy analyses will be performed with use of the ITT population. The per protocol (PP) population will be used for all primary 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. The safety data will be listed and summarized at determined cutoff points, e.g., with use of data for each participant up to Week 96, using all available data at the Week 96 database lock for the primary analysis.

All adverse events will be coded and tabulated by System Organ Class and Preferred Term for individual events within each System Organ Class, 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. Results of C-SSRS will be summarized by treatment group.

Non-MS pathology reported by local safety radiologist will be summarized by treatment group.

Associated laboratory parameters such as hepatic function, renal function and hematology values will be grouped and presented together. Correlation between low IgG and IgM and infections will be presented separately. 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/B-cell depletion will be presented descriptively.

The results of vital sign, physical examination and ECG will be included in individual participant listings. Change from baseline in vital signs will be summarized by groups.

Type I IFN neutralizing antibody data will be summarized in listings and additional analysis will be performed as appropriate.

An external, iDMC will periodically review safety data throughout the study until the primary analysis is performed. Following unblinding after the 96-week period, 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 participants treated with ocrelizumab beyond the double-blind, double-dummy treatment period of the study. The data will be summarized according to the randomized treatment groups of the double-blind, double-dummy treatment period of the study. Details of the statistical analyses will be provided in a separate 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 Modelling (NONMEM) analysis of the sparse PK data. Clearances with associated interparticipant 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 interparticipant 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

The relationship between individual ocrelizumab exposure and selected safety and efficacy parameters will be analyzed and explored, in order to characterize the exposure/dose response curve of ocrelizumab. This may include but is not limited to ARR, T1 and T2 lesions at Week 96, IRRs, infections, and other adverse event or safety parameters of interest. Other exploratory analyses may be performed to assess the possible relationship between PD markers (e.g., CD19 count, PK, and clinical response).

8.2.11.3 Roche Clinical Repository/Protein Biomarker Samples

Additional blood samples for serum and/or plasma analyses 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 RMS 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 Research Biosample Repository

All statistical analyses of biosample testing results will be conducted as exploratory and may include, but may not be limited to, examining possible relationships between disease progression biomarker levels and clinical response.

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 eCRFs. It will be transcribed by the site from the paper source documents onto the eCRF. In addition, EDSS, MSFC, C-SSRS, Karnofsky Performance Status Scale 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/electronic interface and backend checks in the data base will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the site for resolution by the investigator.

Throughout the study the Study Management Team (SMT) will review data according to the EDC Cleaning Process as described in the Data Management Plan.

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 and diseases and the International Non-proprietary Name (INN) 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 throughout the study and make recommendations regarding continuation, termination, or modification of the study. During the double-blind, double-dummy phase of the study, regularly scheduled safety data reviews will occur at least 3 times per year after the first participant is enrolled. The DMC will not continue safety monitoring during the OLE phase.

Any safety event that requires unblinding of study treatment allocation 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.

The details of the DMC roles and responsibilities, scope of work 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 participant. 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. Investigational New Drug Application, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations (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

12.2.1 Study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations], to obtain signed informed consent for the double-blind, double-dummy treatment period and the OLE phase of the study from each participant prior to participating in either the double-blind, double-dummy treatment period or the OLE phase of this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the participants are completely free to refuse to enter any period of 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 risk/benefit 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.

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.

- **For U.S. Investigational New Drug (IND) studies:** in a life-threatening situation where a participant is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the participant's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the participant under protocol with consent of both the investigator and another physician not involved in the study, with appropriate documentation submitted to the IRB within 5 days. If this collaboration is not immediately possible, there must be a written evaluation by a physician independent of the study and the appropriate documentation be submitted to the IRB within 5 days of treating the participant. In addition, the participant or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.
- **For non-U.S. IND studies:** in a life-threatening situation where a participant is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the participant's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the participant under protocol with consent of the investigator, with appropriate documentation that the EC had approved the procedures used to enroll participants in such situations. In addition, the participant or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

12.2.2 Research Biosample Repository Informed Consent

The Informed Consent Form (ICF) will contain a separate section that addresses participation in the RBR. For details on the RBR consent, see Section 5.12.5.

12.2.3 Death or Loss of Competence of Participant who has Donated a Specimen(s) that is Stored in the Roche Clinical Repository

In case the ICF and/or the study protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

In the event of the death of a participant of a Roche Clinical Trial or Experimental Medicine Research study or if a participant is legally incompetent at the time of the specimen and data procurement, or becomes legally incompetent thereafter, applicable provisions as stated for such situations in the respective ICF and/or the study protocol shall become effective and be followed accordingly.

Additional procurement of assent from legally incompetent persons and minors shall take place according to local laws and international best practice, as it applies to the specific case.

12.3 INDEPENDENT ETHICS COMMITTEES AND INSTITUTIONAL REVIEW BOARD

The protocol, informed consent and any accompanying material provided to the participant in the U.S. will be submitted by the investigator to an IRB for review. For European Economic Area (EEA) member states, the Sponsor will submit to the Competent Authority and EC, the protocol and any accompanying material provided to the participant. In both the United States and EEA member states, the accompanying material may include participant information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the participant as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IRB/EC must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the participant after receipt of the IRB/EC approval must also be 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.

Roche shall also submit an Annual Safety Report once a year to the EC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

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 and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent 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, Roche and the investigator will assure that adequate consideration is given to the protection of the participants' interests. The appropriate IRB/EC and Regulatory Agencies should be informed accordingly.

15. STUDY DOCUMENTATION, CASE REPORT FORMS, 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 two different separate categories (1) Investigator's Study File, and (2) participant clinical source documents.

The investigator's Study File will contain the protocol/amendments, eCRF 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 compact disc 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 informed consent forms, consultant letters, and participant screening and enrollment logs.

The investigator must keep the two categories of documents as described above (including the archival compact disc) 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.

International Council for Harmonisation Good Clinical Practice (GCP) guidelines require that investigators maintain information in the study participant's records which corroborate data collected on the eCRF(s). Completed eCRF will be transferred to Sponsor.

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 participant 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 of source documents.

15.4 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an EDC system by with use of eCRFs. 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.
The investigator must update eCRF and connect on a regular basis.

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 (even during a pre-randomization screening period if an eCRF was initiated). 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 events, 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.

15.5 FINANCIAL DISCLOSURE

The investigator(s) will provide the Sponsor with sufficient accurate financial information (Form PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last participant, last visit).

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 in 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 GCP, 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 Case Report Forms (CRFs) 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 Roche, 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 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. CLINICAL STUDY REPORT

A Clinical Study Report will be written and distributed to health authorities as required by applicable regulatory requirements.

19. 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 website:

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 authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche 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 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 2 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 one 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 events electronic form (eForm) of the electronic Case Report Form (eCRF): intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Institutional Review Board/Ethics Committee 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 3 Common Terminology Criteria (CTCAE)

In the present study, toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

The CTCAE v4.0 can be found in the Roche handout entitled: "Common Terminology Criteria for Adverse Events v4.0" or via the following website: https://ctep.cancer.gov.

Appendix 4 Telephone Interviews

The purpose of this interview is 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). Telephone interviews should be performed by study personnel every 4 weeks between clinic visits.

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

Questions	No	Yes
1. **Since your last visit or telephone interview, have you had any new or worsening medical problems (such as sudden changes in your thinking, alterations in your behavior, visual disturbances, extremity weakness, limb coordination problems, or gait abnormalities) that have persisted over more than one day?**		
2. **Since your last visit or telephone interview, have you had any signs of an infection?**		
3. **Since your last visit or telephone interview, have you had any other new or worsening medical problems or conditions (including pregnancy)?**		
4. **Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat cancer or MS, 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 Treating Investigator and review the participant's answers. The investigator can determine if an unscheduled visit is required.

Please report all relevant information in the electronic Case Report Form as well.

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

_____

_____

_____

NAME:_____ Date:_____

Name of person completing the telephone interview

Below is a sample list of medications that can weaken the immune system. This list does not include all drugs that can suppress the immune system.

Approved MS therapies:

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

Immunosuppressants/Antineoplastics:

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

Additional Immunomodulators and Immunosuppressants:

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

- Rituximab (Rituxan/MabThera®)
- Trastuzumab (Herceptin®)

Appendix 5 Modified Fatigue Impact Scale (MFIS)

MFIS

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then SELECT THE ONE NUMBER that best indicates how often fatigue has affected you in this way during the PAST 4 WEEKS. (If you need help in marking your responses, TELL THE INTERVIEWER THE NUMBER of the best response.) PLEASE ANSWER EVERY QUESTION. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the PAST 4 WEEKS....	Never	Rarely	Sometimes	Often	Almost always
* 1. I have been less alert.	0	1	2	3	4
* 2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
* 3. I have been unable to think clearly.	0	1	2	3	4
* 4. I have been clumsy and uncoordinated.	0	1	2	3	4
* 5. I have been forgetful.	0	1	2	3	4
* 6. I have had to pace myself in my physical activities.	0	1	2	3	4

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MFIS

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Because of my fatigue during the PAST 4 WEEKS....	Never	Rarely	Sometimes	Often	Almost always
* 7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
* 8. I have been less motivated to participate in social activities.	0	1	2	3	4
* 9. I have been limited in my ability to do things away from home.	0	1	2	3	4
* 10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
* 11. I have had difficulty making decisions.	0	1	2	3	4
* 12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
* 13. my muscles have felt weak.	0	1	2	3	4
* 14. I have been physically uncomfortable.	0	1	2	3	4

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MFIS

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Because of my fatigue during the PAST 4 WEEKS....	Never	Rarely	Sometimes	Often	Almost always
* 15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
* 16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
* 17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
* 18. my thinking has been slowed down.	0	1	2	3	4
* 19. I have had trouble concentrating.	0	1	2	3	4
* 20. I have limited my physical activities.	0	1	2	3	4
* 21. I have needed to rest more often or for longer periods.	0	1	2	3	4

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Appendix 6 The Center for Epidemiologic Studies Depression Scale (CES-D)

CES-D Scale

Center for Epidemiologic Studies Depression Scale (CES-D, NIMH)

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way in the last week.

	During the Past Week			
	Rarely or none of the time (less than 1 Day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
* 1. I was bothered by things that usually don't bother me.	○	○	○	○
* 2. I did not feel like eating: my appetite was poor.	○	○	○	○
* 3. I felt that I could not shake off the blues even with help from my family or friends.	○	○	○	○
* 4. I felt that I was just as good as other people.	○	○	○	○
* 5. I had trouble keeping my mind on what I was doing.	○	○	○	○
* 6. I felt depressed.	○	○	○	○
* 7. I felt that everything I did was an effort.	○	○	○	○
* 8. I felt hopeful about the future.	○	○	○	○
* 9. I thought my life had been a failure.	○	○	○	○
* 10. I felt fearful.	○	○	○	○

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CES-D Scale

Center for Epidemiologic Studies Depression Scale (CES-D, NIMH)

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way in the last week.

	During the Past Week			
	Rarely or none of the time (less than 1 Day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
* 11. My sleep was restless.	○	○	○	○
* 12. I was happy.	○	○	○	○
* 13. I talked less than usual.	○	○	○	○
* 14. I felt lonely.	○	○	○	○
* 15. People were unfriendly.	○	○	○	○
* 16. I enjoyed life.	○	○	○	○
* 17. I had crying spells.	○	○	○	○
* 18. I felt sad.	○	○	○	○
* 19. I felt that people dislike me.	○	○	○	○
* 20. I could not get "going".	○	○	○	○

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

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Appendix 7 The Short Form-36 (SF-36) Health Survey

SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please SELECT the response that best describes your answer.

* **1. In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
◯ 1	◯ 2	◯ 3	◯ 4	◯ 5

* **2. COMPARED TO ONE YEAR AGO, how would you rate your health in general NOW?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
◯ 1	◯ 2	◯ 3	◯ 4	◯ 5

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SF-36

3. **The following questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
* a. VIGOROUS ACTIVITIES, such as running, lifting heavy objects, participating in strenuous sports.	◯ 1	◯ 2	◯ 3
* b. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	◯ 1	◯ 2	◯ 3
* c. Lifting or carrying groceries.	◯ 1	◯ 2	◯ 3
* d. Climbing SEVERAL flights of stairs.	◯ 1	◯ 2	◯ 3
* e. Climbing ONE flight of stairs.	◯ 1	◯ 2	◯ 3
* f. Bending, kneeling, or stooping.	◯ 1	◯ 2	◯ 3
* g. Walking MORE THAN A MILE.	◯ 1	◯ 2	◯ 3
* h. Walking SEVERAL HUNDRED YARDS.	◯ 1	◯ 2	◯ 3
* i. Walking ONE HUNDRED YARDS.	◯ 1	◯ 2	◯ 3
* j. Bathing or dressing yourself.	◯ 1	◯ 2	◯ 3

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SF-36

4. **During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF YOUR PHYSICAL HEALTH?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
* a. Cut down on the AMOUNT OF TIME you spent on work or other activities.	◯1	◯2	◯3	◯4	◯5
* b. ACCOMPLISHED LESS than you would like.	◯1	◯2	◯3	◯4	◯5
* c. Were limited in the KIND of work or other activities.	◯1	◯2	◯3	◯4	◯5
* d. Had DIFFICULTY performing the work or other activities (for example, it took extra effort).	◯1	◯2	◯3	◯4	◯5

5. **During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
* a. Cut down on the AMOUNT OF TIME you spent on work or other activities.	◯1	◯2	◯3	◯4	◯5
* b. ACCOMPLISHED LESS than you would like.	◯1	◯2	◯3	◯4	◯5
* c. Did work or other activities LESS CAREFULLY THAN USUAL.	◯1	◯2	◯3	◯4	◯5

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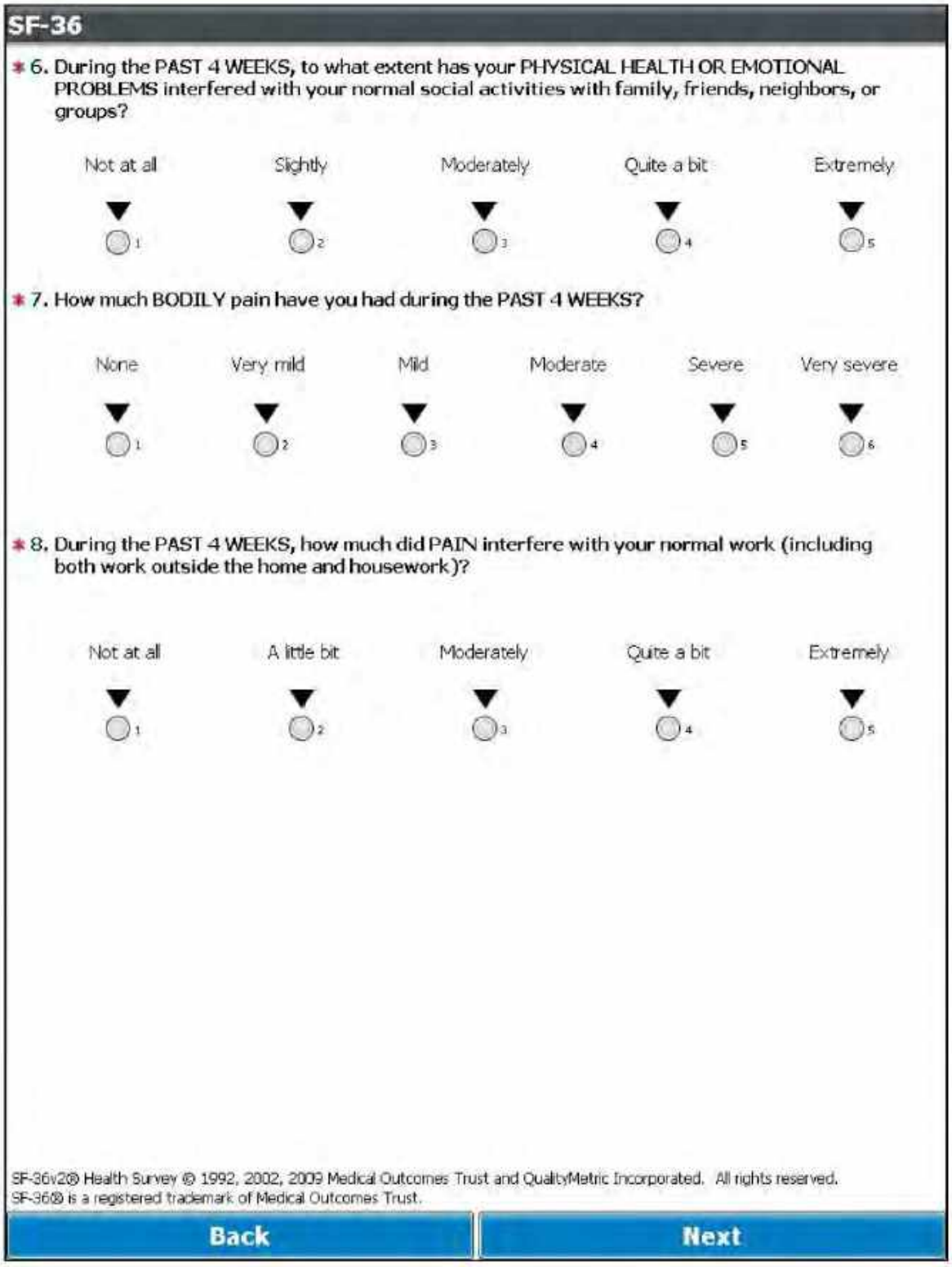

SF-36

* 6. During the PAST 4 WEEKS, to what extent has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all (1) | Slightly (2) | Moderately (3) | Quite a bit (4) | Extremely (5)

* 7. How much BODILY pain have you had during the PAST 4 WEEKS?

None (1) | Very mild (2) | Mild (3) | Moderate (4) | Severe (5) | Very severe (6)

* 8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?

Not at all (1) | A little bit (2) | Moderately (3) | Quite a bit (4) | Extremely (5)

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SF-36

9. These questions are about how you feel and how things have been with you DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
* a. Did you feel full of life?	◯1	◯2	◯3	◯4	◯5
* b. Have you been very nervous?	◯1	◯2	◯3	◯4	◯5
* c. Have you felt so down in the dumps that nothing could cheer you up?	◯1	◯2	◯3	◯4	◯5
* d. Have you felt calm and peaceful?	◯1	◯2	◯3	◯4	◯5
* e. Did you have a lot of energy?	◯1	◯2	◯3	◯4	◯5
* f. Have you felt downhearted and depressed?	◯1	◯2	◯3	◯4	◯5
* g. Did you feel worn out?	◯1	◯2	◯3	◯4	◯5
* h. Have you been happy?	◯1	◯2	◯3	◯4	◯5
* i. Did you feel tired?	◯1	◯2	◯3	◯4	◯5

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SF-36

* 10. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
◯ 1	◯ 2	◯ 3	◯ 4	◯ 5

11. How TRUE or FALSE is EACH of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
* a. I seem to get sick a little easier than other people.	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5
* b. I am as healthy as anybody I know.	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5
* c. I expect my health to get worse.	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5
* d. My health is excellent.	◯ 1	◯ 2	◯ 3	◯ 4	◯ 5

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Appendix 8 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 (Frohman et al. 2008). Optical coherence tomography can be of particular interest in multiple sclerosis (MS), because optic neuritis is 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). The OCT outcome measures such as retinal nerve fiber layer (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 multiple sclerosis (PPMS; Study WA25046).

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 open-label extension (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 600 mg 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 600 mg 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 MS participants 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 MRI
- Confirmed disability progression
- T2 lesion volume
- Number of T1 gadolinium (Gd)-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 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 9).

For participants participating in Studies WA21092 and WA21093:

- The participant should undergo OCT measurement 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 (Week 0; 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, Week 0).

For participants participating in Study WA25046:

- The participant should undergo OCT measurement 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 (Week 0; 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, Week 0).

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 9 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., Studies 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 one 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-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).

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.

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 the schedule of activities (Appendix 9 of this substudy).

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 scheduled visit, the investigator should document all ocular symptoms, including ocular neuritis, in the eCRF 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.

It is possible that the participant withdraws from only the OCT Exploratory substudy. In this case, an OCT Visit should occur if it has not been performed during the previous 4 weeks.

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 Visit 1 (Week 0) and completion/withdrawal visit. This will include best corrected visual acuity evaluation (with Early Treatment Diabetic Retinopathy Study standardized eye chart); color vision test (Hardy Rand Rittler pseudoisochormatic 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. Visual evoked potential measurement should occur during OCT Visit 1 (Week 0). 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 (Week 0).

Optical Coherence Tomography

Optical coherence tomography images will be acquired in all participants as detailed in the schedule of activities (Appendix 9 of this substudy). 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 (Week 0) should occur prior to baseline visit of the primary study and at Visit 2 (Week 24), Visit 3 (Week 48), Visit 4 (Week 72), and Visit 5 (Week 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.
- If a participant enrolls into the OLE phase of the main study, OCT assessments should continue to occur every 24 weeks.

During OCT Visit 1 (Week 0), 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 Independent Review Charter (IRC).

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 participant is participating, as well as the Sponsor. Please see 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 IRC charter.

Sample Size

A total of approximately 300 participants will be enrolled in this substudy.

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 Gd-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.

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Appendix 9 Optical Coherence Tomography Exploratory Substudy Schedule of Activities

	Treatment Period [a]								
Visit	1	2	3	4	5	Open-Label Extension Phase (for OPERA study) [e]	Completion Visit	Safety Follow-Up	Withdrawal Visit [a]
Week (window in days)	0	24 (± 14)	48 (± 14)	72 (± 14)	96 (± 14)				
Informed consent	x								
Ophthalmological and Eye Examination	x						x		x
Visual Evoked Potential	x								
Medical History	x								
Baseline Conditions	x								
OCT [b]	x	x	x	x	x	x	x	x [c]	x
Adverse events [d]	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] 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.

[c] Safety follow-up: OCT assessment should continue every 24 weeks counting after last OCT assessment visit.

[d] Any adverse events should be reported to the Principal Investigator of the study.

[e] If a participant enrolls in the OLE phase of the main study, OCT assessments should occur every 24 weeks.

Appendix 10 Abbreviations

Abbreviation or Term	Definition
23-PPV	23-valent pneumococcal polysaccharide
9HPT	9-Hole Peg Test
ADA	anti-drug antibody (also known as human anti-human antibody [HAHA])
ADCC	antibody-dependent cellular cytotoxicity
ARR	annualized relapse rate
AUC	area under the concentration-time curve
BCG	Bacille Calmette-Guérin
CAs	Competent Authorities
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CDP	confirmed disability progression
cDNA	complementary DNA
CDR3	third complementarity determining region
CES-D	Center for Epidemiologic Studies Depression Scale
CFR	Code of Federal Regulations
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DMT	disease-modifying therapy
EC	Ethics Committee
EEA	European Economic Area
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eForm	Electronic form
ePRO	electronic participant-reported outcomes
ESF	Eligibility Screening Form
FACS	fluorescence-activated cell sorting
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
FSH	follicle-stimulating hormone
FSS	Functional Systems Scale

Abbreviation or Term	Definition
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma glutamyl transferase
HAHA	human anti-human antibody (also known as anti-drug antibody [ADA])
HAM	human T-lymphotropic virus type 1 associated myelopathy
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HepCAb	hepatitis C antibody
HDHF	high-dose high-frequency
hCG	human chorionic gonadotropin
HTLV-1	human T lymphotropic virus type 1
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
IM	intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
JCV	John Cunningham virus
KFS	Kurtzke Functional Systems
KLH	keyhole limpet haemocyanin
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
MTX	methotrexate
NEDA	no evidence of disease activity

Abbreviation or Term	Definition
NONMEM	Nonlinear Mixed Effects Modelling
OCB	oligoclonal band
OCT	optical coherence tomography
OLE	open-label extension
PASAT	Paced Auditory Serial Addition Test
PCR	polymerase chain reaction
PCS	Physical Component Summary
PML	progressive multifocal leukoencephalopathy
PP	per protocol (population)
PPMS	primary progressive multiple sclerosis
PRO	participant-reported outcome
PY	participant-year
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RCR	Roche Clinical Repository
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
RNFL	retinal nerve fiber layer
ROW	Rest of World
RPR	rapid plasma reagin
RR	relative reduction
RRMS	relapsing-remitting multiple sclerosis
S1P	sphingosine-1 phosphate
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDMT	Symbol Digit Modalities Test
SF-36	Short Form-36 Health Survey
SMT	Study Management Team
SPMS	secondary progressive multiple sclerosis
T25FWT	Timed 25-Foor Walk Test
TB	tuberculosis
TT	tetanus toxoid
ULN	upper limit of normal
USPI	U.S. Package Insert
VH4	variable heavy 4
VLA-4	α-4 β-1 integrin