Official Title: A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis

NCT Number: NCT04035005

Document Date: Protocol Amendment Version 6: 04-Jul-2024

PROTOCOL

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	WA40404
VERSION NUMBER:	6
EU CT NUMBER:	2023-505980-36-00
EUDRACT NUMBER:	2018-001511-73
IND NUMBER:	100,593
NCT NUMBER:	NCT04035005
TEST PRODUCT:	Ocrelizumab (RO4964913) (OCREVUS®)
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
6	See electronic date stamp on the final page of this document.	—	—	—
5	13 October 2022	—	—	—
4	1 February 2021	—	—	—
3	4 August 2020	—	—	—
2	12 March 2020	—	—	—
1	14 February 2019	Italy	1	13 August 2019
		Ireland	1	30 June 2019
		United Kingdom	1	26 June 2019

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol WA40404 has been amended primarily to update the trial objectives, update the duration of follow-up 2 (FU2) and remove the B-cell monitoring (BCM) phase. Changes to the protocol, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with E.U. CTR and other guidelines.
- The primary efficacy objective and the timing of the primary analysis has been updated to reflect current planned analyses. In order to better capture the spectrum of disability progression, and in line with the current trend towards composite disability endpoints being used as primary endpoints in several ongoing pivotal MS trials, the Sponsor combined the primary and key secondary endpoint into a composite endpoint (Sections 1.3, 2.1.1, 2.5, 3.1, 3.5 and 6.4.1.1).
- The secondary efficacy objective has been updated to reflect current planned analyses (Sections 1.3, 2.1.2, 2.5, 3.5 and 6.4.1.2).
- Additional exploratory efficacy objectives have been updated to reflect current planned analyses (Sections 2.1.3 and 6.4.3).
- The FU2 phase has been shortened to 24 weeks for each patient (Section 3.1.1.6, 3.2 and Appendix 4) and the BCM phase has been removed (Sections 3.1, 3.2, 3.5, 5.1.1.1, 5.4.2.2, 5.5.2 and Appendix 4) as the safety profile of ocrelizumab is well established and does not warrant 48 weeks follow-up and BCM phase. In addition, shortening the FU2 and BCM phase will avoid delaying patient access to post study treatment. As a result, the end of study and length of study section has been updated (Section 3.2).
- A section describing duration of participation has been added to align with E.U. CTR requirements (Section 3.3).
- Text has been added to allow patients to be premedicated with an oral dose of prednisolone or methylprednisolone, should IV methylprednisolone not be available (Sections 3.5.4 and 4.3.2.2, Appendix 1 and 2).
- Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial. A rationale has been provided in Section 3.4.6.
- The language regarding single-patient, emergency and non-emergency unblinding requested by the investigator has been updated to align with internal procedures (Section 4.2).
- Text has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 4.3.4).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The biomarker analyses have been simplified in the protocol as the details are described in the statistical analysis plan and biomarker analysis plan. (Section 6.8).

- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with E.U. CTR requirements (Appendix 14).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
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TEST PRODUCT:	Ocrelizumab (RO4964913) (OCREVUS®)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or their designee.

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with PPMS, including patients later in their disease course.

1.1.1 *Primary and Secondary Objectives and Endpoints*

Primary Objective	*Corresponding Endpoint*
• *Evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients and in patients with MRI activity (MRI activity is defined as presence of T1 Gd+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase)*	*Time to onset of composite 12-week CDP defined as the time from randomization to the first occurrence of at least one of the following progression events:* • *12-week CDP in 9-HPT, defined as a 20% worsening from baseline in 9-HPT confirmed for at least 12 weeks* • *12-week CDP in EDSS score, defined as an increase of ≥1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤ 5.5 or an increase of ≥0.5 point in patients with a baseline EDSS score of <5.5 that is confirmed for at least 12 weeks*

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MRI = magnetic resonance imaging.

Secondary Objectives	*Corresponding Endpoints*
• *Evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients*	• *Time to 12-week CDP in 9-HPT* • *Time to 12-week CDP in EDSS* • *Time to 24-week CDP in 9-HPT* • *Time to 24-week CDP in EDSS* • *Annual rate of percent change from baseline in total volume of T2 lesions* • *Annual rate of percent change from Week 24 in total brain volume*
Safety Objective	*Corresponding Endpoints*
• *Evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other DMT for MS*	• *See Section 6.5 of the protocol.*
Immunogenicity Objective	*Corresponding Endpoints*
• *Immunogenicity, as the presence of ADA during the study relative to baseline*	• *See Section 6.7 of the protocol.*
Pharmacokinetic Objectives	*Corresponding Endpoints*
• *Characterization of the ocrelizumab PK profile* • *Evaluation of ocrelizumab pharmacodynamics, as measured by B-cell levels in blood*	• *See Section 6.6 of the protocol.*

9-HPT = 9-Hole Peg Test; ADA =anti-drug antibody; CDP = confirmed disability progression; DMT =disease-modifying therapy; EDSS = Expanded Disability Status Scale; Gd = gadolinium; MS =multiple sclerosis; MRI = magnetic resonance imaging; PK =pharmacokinetic.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 6.

1.1.2 *Overall Trial Design*

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase IIIB*	***Population Type:***	*Adult patients*
Control Method:	*Placebo-controlled*	***Population Diagnosis or Condition:***	*PPMS*
Interventional Model:	*Randomization*	***Population Age:***	*18–65 years*
Test Product:	*Ocrelizumab*	***Site Distribution:***	*Multi-region*
Active Comparator:	*Not applicable*	***Trial Intervention Assignment Method:***	*Randomization*
Number of Arms:	*2 arms*	***Number of Participants to Be Enrolled:***	*Approximately 1000, with at least 350 in the MRI active subgroup*

Study Treatment

The ocrelizumab (or placebo) dose administered will be 600 mg every 24 weeks. The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab will be administered as a single 600 mg infusion every 24 weeks. A minimum interval of 20 or 22 weeks, depending on if the previous dose was administered in one or two infusions, should be maintained between each infusion.

Duration of Total Trial Participation

The total duration of study participation for an individual is expected to be approximately up to 10.5 years.

Total Planned Duration of Trial Intervention

The total duration of study treatment for an individual is expected to be approximately up to 10.5 years.

Blinded Roles

Investigators, site personnel, participants and the Sponsor will not be made aware of treatment group assignment during the study.

Committees

Independent Committees:	*Independent Data Monitoring Committee*
Other Committees:	*External Steering Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
9-HPT	9-Hole Peg Test
ADA	anti-drug antibody
ADL	activities of daily living
ANCOVA	analysis of covariance
BCM	B-cell monitoring
CDP	confirmed disability progression
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DMT	disease-modifying therapy
DPE	double-progression event
DSS	Disability Status Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FSS	Functional System Scores
FU1	follow-up 1
FU2	follow-up 2
Gd	gadolinium
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system

Abbreviation	Definition
JC	John Cunningham
MFIS	Modified Fatigue Impact Scale
MMRM	mixed effect model repeat measurement
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS	Multiple Sclerosis Impact Scale
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-QoL-UE	Quality of Life in Neurological Disorders-Upper Extremity Function
NfL	neurofilament light chain
OLE	open-label extension
PDP OCR	post-double-progression ocrelizumab
PGIC	Patient Global Impression of Change
PGIC-F	Patient Global Impression of Change for fatigue
PGIC-UL	Patient Global Impression of Change for upper limb function
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPMS	primary progressive multiple sclerosis
PRO	patient-reported outcome
PY	patient years
QoL	quality of life
RBR	Research Biosample Repository
RCRM	*random coefficient regression model*
RMS	relapsing multiple sclerosis
RPM	remote patient monitoring
RRMS	relapsing-remitting MS
SAP	*Statistical Analysis Plan*
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDMT	Symbol Digit Modalities Test
SmPC	summary of product characteristics
ULN	upper limit of normal
USPI	U.S. prescribing information
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the CNS that affects approximately 2.3 million people worldwide (MSIF 2013). While MS is a global disease, its prevalence is highest in North America and Europe (140 and 108 per 100,000 people, respectively) (MSIF 2013). MS is commonly diagnosed during reproductive age, between 20 and 40 years (Tullman 2013). Overall, MS is approximately twice as prevalent in women as in men, except in individuals with the primary progressive- form of the disease, where there is no gender prevalence difference (MSIF 2013; Tullman 2013). Reasons for these observed differences are unclear. However, progression, once it begins, continues at similar rates in women and men (Leray et al. 2010).

In approximately 85% of patients, MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery (referred to as relapsing-remitting MS [RRMS]). If left untreated, the majority of these patients will transition to a progressive form characterized by worsening neurologic disability, either with or without occasional super-imposed relapses (relapsing or non-relapsing secondary progressive MS). Patients accumulate disability as a result of incomplete recovery from acute relapses and/or gradual disease progression (Tullman 2013). Primary progressive MS (PPMS) is a less common form of MS, accounting for approximately 10% of all cases (approximately 40,000 individuals in the United States). PPMS is characterized by a progressive course from disease onset, with infrequent superimposed discrete clinical attacks or relapses (Lublin et al. 2014). Unlike RRMS, the typical age of onset for PPMS is older at approximately 40 years, and men are affected nearly as often as women (Cottrell et al. 1999). The absence of relapses imposes special challenges for diagnosis, requiring clinical evidence that the disease has advanced for at least 1 year from symptom onset independent of clinical relapse (Thompson et al. 2018).

Natural history studies of patients with PPMS suggest a disabling course from symptom onset. In a well-characterized cohort of patients with PPMS from Ontario, Canada, the median time to the use of a unilateral cane or brace (Disability Status Scale [DSS] or DSS 6) was 8 years and the median time to wheelchair use (DSS 7) was under 20 years (Cottrell et al. 1999). A higher proportion of patients with PPMS present initially with motor impairment, cerebellar ataxia, and brainstem symptoms than relapsing-onset patients, and spastic paraparesis is a common early clinical presentation (Andersson et al. 1999). Evidence suggests that inflammation is present in the CNS throughout all MS clinical courses, from RRMS to secondary progressive MS, and in PPMS (Frischer et al. 2009). Differences between disease phenotypes are due to the differential contribution of each of the inflammatory and neurodegenerative processes to the pathophysiology of CNS damage over time (Frischer et al. 2009, 2015).

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre-B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Based on the results of ocrelizumab Phase III studies in patient populations with relapsing MS (RMS) and PPMS, ocrelizumab was approved by the US Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS and by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of MS defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Two identical randomized, active-controlled studies (OPERA I [Study WA21092] and OPERA II [Study WA21093]) have demonstrated superior efficacy outcomes versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy in PPMS versus placebo (Montalban et al. 2017). Results of these studies show that depletion of CD20+ B cells leads to a significant impact on a broad range of clinical measures of disease, including disability progression, in addition to an impact on magnetic resonance imaging (MRI) outcomes related to disease progression and reflective of neural tissue loss, thus further supporting the hypothesis that B cells are central to the pathogenesis of both RMS and PPMS. Ocrelizumab has demonstrated a favorable safety profile in patients with RMS and PPMS (Hauser et al. 2017; Montalban et al. 2017). The proportion of patients with adverse events was similar in patients treated with ocrelizumab compared with interferon β-1a (both 83.3%) or placebo (95.1% vs. 90.0%). The proportion of patients experiencing a serious adverse event was similar between ocrelizumab and the comparator groups (in RMS: 6.9% [ocrelizumab] and 8.7% [interferon β-1a]; in PPMS: 20.4% [ocrelizumab] and 22.2% [placebo]).

Refer to the Ocrelizumab Investigator's Brochure and/or local prescribing information for details on nonclinical and clinical studies of ocrelizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The pivotal Phase III Study WA25046 (ORATORIO) was a global, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial evaluating the efficacy and safety of ocrelizumab in adults with PPMS. The primary endpoint was the time to onset of confirmed disability progression (CDP) during the treatment period, defined as an increase in the Expanded Disability Status Scale (EDSS) score that was sustained for at least 12 weeks. Disability was assessed using the EDSS (Kurtzke 1983). In Study WA25046, an event of disability progression was defined as an increase from

baseline EDSS of 1 point or more for patients with a baseline EDSS score of ≤5.5, or an increase of 0.5 point or more for patients with a baseline EDSS score of >5.5. This sustained increase in EDSS is considered a clinically meaningful change as described in the EMA MS Guideline of 2015 (EMA 2015). Study WA25046 met its primary endpoint (24% reduction in the risk of 12-week CDP compared with placebo [hazard ratio=0.76; 95% CI: 0.59, 0.98; p=0.0321]) and demonstrated significant reduction in both clinical and subclinical measures of disease progression compared with placebo. In Study WA25046, the results of the 9-Hole Peg Test (9-HPT), a pre-specified exploratory endpoint, showed a significant 44% reduction in progression for patients treated with ocrelizumab versus placebo (p=0.0004) (see Table 1 below and Section 5.1 in the Primary Clinical Study Report for Study WA25046*). In a post-hoc exploratory analysis, the results of the composite 12-week CDP of EDSS and 9-HPT showed a significant 25% reduction in disability progression for patients treated with ocrelizumab versus placebo (p=0.0136) (Table 1).*

Table 1 Analysis of Time to 12-Week Confirmed 20% Increase in 9-HPT Score *and Time to Composite 12-Week Confirmed Disability Progression of EDSS and 9-HPT* (All Randomized Patients: Study WA25046)

Endpoint	Patients with Event		Hazard Ratio (95% CI)	p-value (log-rank)
	Placebo (N=244)	Ocrelizumab (N=488)		
20% increase in 9-HPT confirmed at 12 weeks	66/244	83/488	0.56 (0.41, 0.78)	0.0004
Composite 12-week CDP of EDSS and 9-HPT	*119/244*	*199/488*	*0.75 (0.60, 0.95)*	*0.0136*

9-HPT=9-Hole Peg Test; *CDP=Confirmed Disability Progression; EDSS=Expanded Disability Status Scale.*

Source: Unpublished data.

Study WA25046 included patients aged 18–55 years with a baseline EDSS score ranging from 3.0 to 6.5. Within this population, patients with more advanced disability consisting of EDSS score ≥5.5 and patients with an abnormal 9-HPT time of >25 seconds at baseline showed more rapid rates of upper limb disability progression on the 9-HPT. In the post-hoc analyses of these more advanced subgroups of patients, ocrelizumab showed a significant 44% reduction in 20% 9-HPT progression versus placebo (p=0.0085 and p=*0.0023*, respectively) (see Table 2). EDSS score >5.5 corresponds to patients with lower extremity impairment requiring unilateral assistance (e.g., cane or crutch) with or without upper extremity impairment. Thus, the Study WA25046 results imply that ocrelizumab may reduce the rate of progression of upper limb disability in patients even if significant lower extremity disability has ensued. 9-HPT times above a threshold of 25 seconds can be regarded as abnormal based on

a reference population of patients aged 18–59 years (consistent with the age of the ORATORIO population) from a large-scale normative database (N = 4319) (Wang et al. 2015). Patients with an abnormal 9-HPT time of >25 seconds at baseline progressed more rapidly than patients with normal 9-HPT time of ≤25 seconds; however, both patient groups showed a comparable benefit from treatment with ocrelizumab (44% [hazard ratio=0.56; 95% CI: 0.38, 0.82; p=0.0023] and 49% [hazard ratio=0.51; 95% CI: 0.27, 0.97; p=0.0358] risk reduction, respectively) (see Table 2). Presence of inflammatory activity as detected by mandatory MRI at baseline correlates with a greater treatment benefit. Pre-specified, non-powered, subgroup analysis of the primary endpoint (time to 12-week CDP progression) in Study WA25046 suggests that patients with T1 gadolinium (Gd)-enhancing lesions at baseline received a greater treatment benefit than patients without T1 Gd-enhancing lesions (with T1 Gd-enhancing lesions at baseline: HR=0.65 [95% CI: 0.40–1.06], without T1 Gd-enhancing lesions at baseline: HR = 0.84 [95% CI: 0.62–1.13]; EMA 2018). With regard to inflammatory activity and hand function, ocrelizumab-treated patients with MRI-detected T1 Gd-enhancing lesions at baseline experienced a significant 58% reduction in 20% 9-HPT progression versus placebo (p=0.0034); a reduction of 36% (p=0.0242) in 20% 9-HPT progression versus placebo was observed in ocrelizumab-treated patients without MRI-detected T1 Gd-enhancing lesions at baseline (see Table 2).

Table 2 Analysis of Time to 12-Week Confirmed 20% Increase in 9-HPT Score *and Time to Composite 12-Week Confirmed Disability Progression of EDSS and 9-HPT* by Population (All Randomized Patients: Study WA25046)

Population	Percent of Patients with Event at Week 120 (Placebo Arm)[a]	Percent of Patients with Event at Week 120 (Ocrelizumab Arm)[a]	Hazard Ratio (95% CI)	p-value (log-rank)
12-week confirmed 20% increase in 9-HPT				
EDSS ≥5.5	39%	21%	0.56 (0.36, 0.87)	0.0085
T1 Gd+	39%	16%	0.42 (0.23, 0.76)	0.0034
T1 Gd–	18%	14%	0.64 (0.43, 0.95)	0.0242
9-HPT >25 seconds	33%	18%	0.56 (0.38, 0.82)	0.0023
9-HPT ≤25 seconds	12%	9%	0.51 (0.27, 0.97)	0.0358
Composite 12-week CDP of EDSS and 9-HPT				
EDSS ≥5.5	*58%*	*46%*	*0.75 (0.53, 1.05)*	*0.0927*
T1 Gd +	*54%*	*39%*	*0.66 (0.43, 1.04)*	*0.0693*
T1 Gd –	*40%*	*36%*	*0.81 (0.62, 1.06)*	*0.1184*
9-HPT >25 seconds	*55%*	*41%*	*0.69 (0.52, 0.91)*	*0.0083*
9-HPT ≤25 seconds	*31%*	*31%*	*0.83 (0.56, 1.22)*	*0.3359*

9-HPT = 9-Hole Peg Test; EDSS = Expanded Disability Status Scale; Gd = gadolinium; *CDP = Confirmed Disability Progression.*

[a] Kaplan-Meier estimates.

Source: Unpublished data.

Therefore, given the encouraging results from Study WA25046, the primary objective of this study is to evaluate the efficacy of ocrelizumab compared with placebo on the *composite 12-week CDP of EDSS and 9-HPT* in a population that also includes patients with more advanced PPMS who acquired significant lower extremity impairment. The study will include patients with a baseline EDSS score from 3.0 to 8.0, inclusive. *CDP in* upper limb function using the same 9-HPT measure that was used in Study WA25046 *will also be evaluated as a key secondary objective.* Moreover, the upper limit of age of the enrolled population will be 65 years, and the treatment effect of ocrelizumab will be explored according to the presence of inflammatory activity as detected by mandatory MRI at baseline. Additional secondary and exploratory objectives will evaluate the efficacy of ocrelizumab on its ability to reduce disease progression on other clinical and subclinical measures. These will include clinical measures of other neurological functional systems, subclinical imaging and biomarker measures, and measures of fatigue and quality of life.

1.3.1 Clinical Relevance of Upper Extremity Disability Progression, as Measured by the 9-HPT, in PPMS

Patients with PPMS with high EDSS scores, including those who are wheelchair-restricted, have a devastating reduction in quality of life if they lose any residual function in their arms and/or hands. For this reason, preserving upper limb function is highly relevant to the quality of life of the patient and an important therapeutic clinical goal in PPMS. Dysfunction of the upper limbs is clinically relevant as it significantly limits the ability to perform activities of daily living, affects the level of independence, and negatively impacts quality of life (Kraft et al. 2014). Patients with more advanced PPMS have been recognized as a much-underserved population with very limited therapeutic options (Kraft et al. 2014). Therefore, exploring the therapeutic effects of ocrelizumab in this PPMS population will be both consistent with and expand on the results of Study WA25046 as well as fulfill a significant medical need for these patients.

The 9-HPT has become one of the most frequently used measures of upper extremity function in MS (Earhart et al. 2011). The 9-HPT provides a brief, standardized approach to assess upper limb function and can be administered by a wide variety of trained examiners (Earhart et al. 2011). The test has high inter-rater reliability and good test-retest reliability (Erasmus et al. 2001). There is also evidence for concurrent and convergent validity as well as sensitivity to detect minor impairments of hand function (Parker et al. 1986; Wang et al. 2015). A 20% worsening in test time is commonly used to define clinically meaningful worsening (Feys et al. 2017) as it corresponds to

predefined clinically meaningful changes of established clinician and patient-reported measures.

1.3.2 Benefit-Risk Assessment of the Conduct of the Study during the COVID-19 Pandemic

A benefit-risk assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the conduct of this study. Based on that assessment, no impact is anticipated, and the existing information on identified and potential risks, safety monitoring, and management guidelines and risk mitigation measures provided in the study protocol are considered adequate.

The available safety data from patients with MS treated with ocrelizumab to date suggests that severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infections follows a similar course in these patients as in the general population, with risk factors for severe SARS-COV-2 infections that are similar in the general population, the overall MS population, and in those treated with ocrelizumab (Hughes et al. 2021).

The protocol's eligibility criteria mitigate the known risk factors for severe SARS-COV-2 infection outcomes, such as older age, more advanced MS disease status, and presence of relevant comorbidities, and exclude patients with MS with any known or suspected active infection (including SARS-CoV-2, based on the investigator's assessment) from participating in the study. As per Section 4.3.2.3, absence of active infection is also required for patients to receive further re-treatment with ocrelizumab. The risk of MS progression may potentially increase over time, if highly effective treatments are delayed.

In summary, protocol-mandated safety monitoring and management guidelines, study eligibility criteria, and ocrelizumab re-treatment criteria are considered adequate in the context of conducting the study during the COVID-19 pandemic. Investigators should manage SARS-CoV-2 infection in the same way as infections caused by any other pathogen, as per local guidelines.

1.3.3 Benefit-Risk Assessment for Concomitant Use of COVID-19 Vaccines

A benefit-risk assessment was conducted to determine whether there is any impact on the concomitant use of COVID-19 vaccines on the conduct of this study. Based on this assessment, no interaction between the concomitant use of COVID-19 vaccines and ocrelizumab has been identified. There is no anticipated impact affecting the efficacy and safety of ocrelizumab in patients enrolled in ocrelizumab clinical trials. Existing key safety information as described in the protocol (namely immunizations [see Section 4.4.4], and impaired response to vaccination [see Section 5.1.1.1]), safety monitoring, and risk mitigation measures related to administration of vaccines (including COVID-19 vaccines) are considered adequate.

As described in Section 5.1.1.1 (impaired response to vaccination), data from the pivotal Phase III studies (WA21092/93, WA25046) of ocrelizumab in RMS and PPMS show that preexisting humoral immunity to common viral and bacterial antigens is not affected by ocrelizumab treatment. Additionally, for patients receiving vaccines while treated with ocrelizumab, the vaccination study BN29739 (VELOCE) showed that patients 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 in patients who received ocrelizumab, albeit with reduced levels of antibodies compared to patients in the control arm. Vaccines were given as early as 12 weeks following the first ocrelizumab infusion (as early as 10 weeks following the second ocrelizumab infusion of the first dose). Booster doses were given at least 4-weeks before the next dose of ocrelizumab. Other immune responses, such as cellular responses, were not investigated in the VELOCE study.

The Sponsor is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the COVID-19 vaccines in patients treated with ocrelizumab.

As with any other medication or vaccine, COVID-19 vaccines should be reported as concomitant medications by using the standard fields in the clinical database (see immunizations [see Section 4.4.4], and medical history, baseline conditions, concomitant medications, and demographic data [see Section 4.5.2]).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of ocrelizumab (Ocrevus®) compared with placebo in patients with PPMS, including patients later in their disease course. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients and in patients with MRI activity (MRI activity is defined as presence of T1 Gd+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase) *on the basis of the following endpoint:*

Time to onset of composite 12-week CDP defined as the time from randomization to the first occurrence of at least one of the following progression events:

- *12-week CDP in 9-HPT, defined as a 20% worsening from baseline in 9-HPT confirmed for at least 12 weeks*
- *12-week CDP in EDSS score, defined as an increase of ≥1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤5.5 or an increase*

of ≥0.5 point in patients with a baseline EDSS score of >5.5 that is confirmed for at least 12 weeks

The estimand of this endpoint will be discussed in Section 6.4.1.1.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the endpoints below, in hierarchical order. The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI-active subgroup.

- *Time to 12-week CDP in 9-HPT*
- Time to 12-week CDP in EDSS
- *Time to 24-week CDP in 9-HPT*
- Time to 24-week CDP in EDSS
- *Annual rate of* percent change *from baseline* in total volume of T2 lesions
- *Annual rate of* percent change *from Week 24* in total brain volume

The estimand for the secondary endpoint of time to 12-week CDP in 9-HPT and time to 12-week CDP in EDSS is described in Sections 6.4.1.2.1 and 6.4.1.2.2, respectively.

2.1.3 Exploratory Efficacy Objective

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo in patients, as measured by the primary and secondary endpoints in the following patient subgroups:

- Age >55 versus ≤55
- EDSS score ≤6.5 versus >6.5
- MRI-inactive versus MRI-active
- Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup)

Additional exploratory objectives include the efficacy of ocrelizumab compared with placebo in patients from all randomized patients and the MRI-active subgroup as measured by the following endpoints:

- Change from baseline to Week 120 in fatigue as measured by Modified Fatigue Impact Scale (MFIS)
- *Annual rate of percent change* from baseline and from Week 24 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)

- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Quality of Life in Neurological Disorders-Upper Extremity Function [Neuro-QoL-UE])
- Change from baseline to Week 120 in the Patient Global Impression of Change for upper limb function (PGIC-UL)
- Change from baseline to Week 120 in the Patient Global Impression of Change for fatigue (PGIC-F)
- Change from baseline to Week 120 in the Multiple Sclerosis Impact Scale (MSIS)29 physical score
- Proportion of patients at Week 120 with a clinically meaningful decline on the MSIS-29
- Change from baseline to Week 120 in the Symbol Digit Modalities Test (SDMT)
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight remote patient monitoring [RPM])
- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI
- *Annual rate of percent* change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain

2.2 SAFETY OBJECTIVES

The safety objectives for this study are to evaluate the safety of ocrelizumab compared with placebo, as well as over time, for all patients who received ocrelizumab and until they receive any other DMT for MS.

Safety endpoints considered include adverse events, serious adverse events, adverse events leading to study treatment withdrawal, vital signs, change from baseline in laboratory test results, association of decrease in certain laboratory parameters, and serious infections. For details on the analyses and the population, see Section 6.5.

2.3 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective is as follows:

- Immunogenicity, as the presence of anti-drug antibody (ADA) during the study relative to baseline. The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy, and safety may be explored.

2.4 PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

The pharmacokinetic (PK) and pharmacodynamic objectives are as follows:

- Characterization of the ocrelizumab PK profile
- Evaluation of ocrelizumab pharmacodynamics, as measured by B-cell levels in blood

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to ocrelizumab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint*s*:

- Neurofilament light chain (NfL) levels (actual value and percentage change from baseline) at each visit up to time of clinical cutoff of primary analysis
- The prognostic or predictive relationship between baseline NfL and *efficacy (including the study primary endpoint, imaging, or key secondary endpoints)*
- The prognostic relationship between on-treatment NfL (measured at Weeks 24 or 48) and subsequent disability progression on the *study primary endpoint and other* clinical outcomes
- Relationship between biomarkers in blood (plasma and/or serum) and/or cerebrospinal fluid (CSF) (listed in Section 4.5.11) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with ocrelizumab on the basis of the following endpoint:

- Relationship between EQ-5D-5L index score and clinical measurements that may support pharmacoeconomic modeling

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study WA40404 is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy and safety of ocrelizumab administered at a 600 mg IV infusion every 24 weeks in patients with PPMS, including patients later in their disease course. This study will consist of the following phases: screening, double-blind treatment, an optional post-double-progression ocrelizumab (PDP OCR) treatment, follow-up 1 (FU1), an optional open-label extension (OLE), *and* follow-up 2 (FU2).

Patients providing informed consent will undergo screening prior to the study drug administration. Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab. Randomization will be performed through an interactive voice or web-based response system (IxRS).

The expected sample size will be approximately 1000 patients, with at least 350 patients in the MRI-active subgroup. The MRI-active subgroup will consist of patients with T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening. If during the study conduct more than 650 patients have enrolled without MRI activity (referred to as MRI-inactive subgroup thereafter), then subsequently only patients with MRI activity may be enrolled to ensure that at least 350 patients with MRI activity will be randomized.

Patients will be treated for 144 weeks (6 study drug doses, with each dose 24 weeks apart) in the double-blind treatment phase *or until the primary analysis, whichever occurs earlier*. The primary analysis will be performed after the last randomized patient reaches 144 weeks of double-blind treatment (+ 12 weeks to allow for the confirmation of the latest event) *or when at least 340 events are reached, whichever occurs earlier*. Patients who experience a double-progression event (DPE; defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks) during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment and 120-week visit assessments. See Section 3.1.1.3 for definitions of DPE and PDP OCR.

Patients will be recruited globally. Patients who prematurely discontinue from study treatment will continue to be followed in the FU1 phase until 144 weeks from randomization for each patient *or until the primary analysis, whichever occurs earlier* (see Section 3.1.1.4).

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed. Monitoring details will be described in the iDMC Charter.

Figure 1 presents an overview of the study design. Figure 2 shows the patient progression through the study. The schedules of activities are provided in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. Overview of the dosing regimen across study phases is provided in Table 3.

Figure 1 Study Design

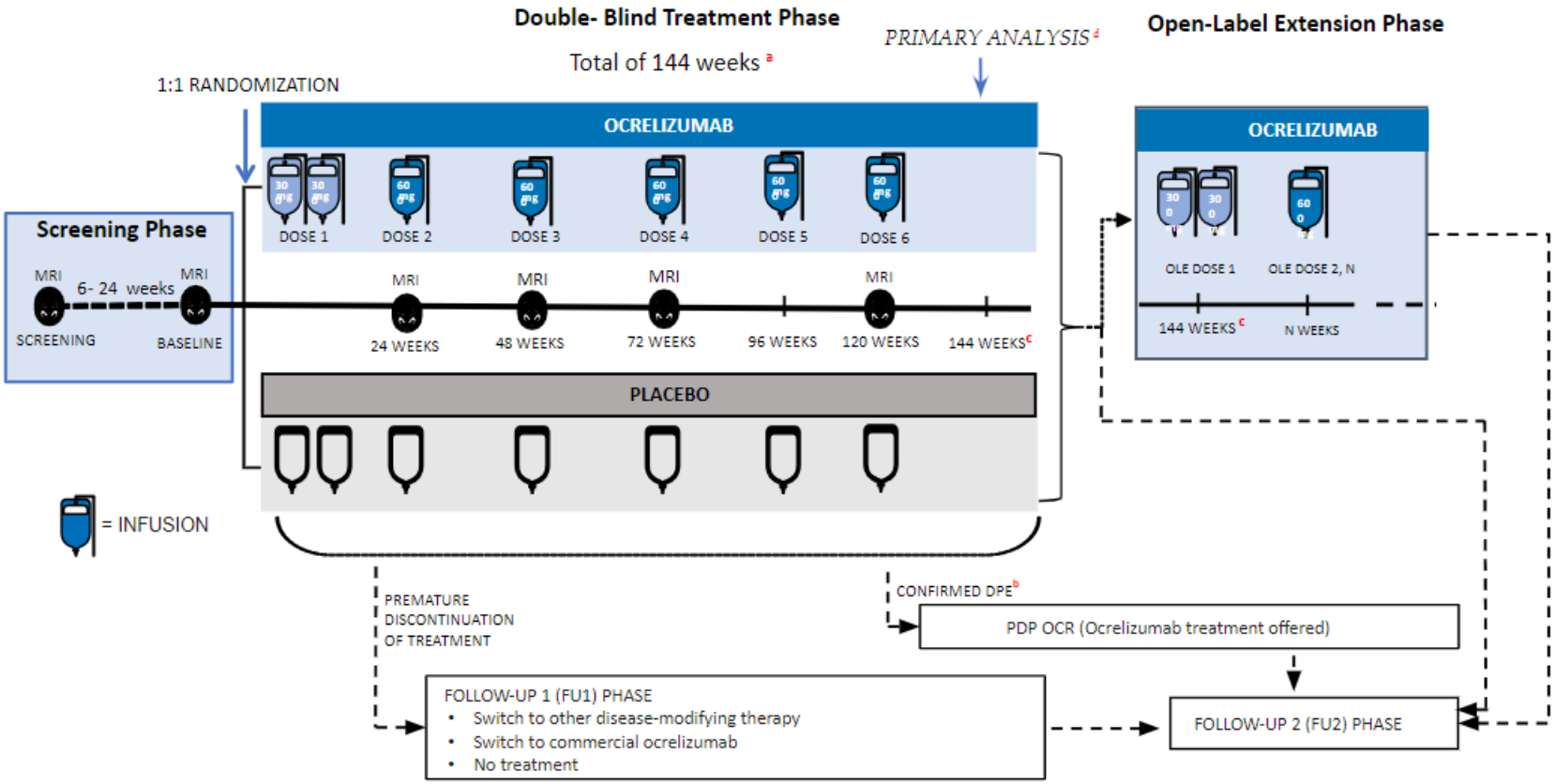


Figure 1 Study Design (cont.)

DPE = double-progression event; FU1 = follow-up 1; FU2 = follow-up 2; MRI = magnetic resonance imaging; OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab.

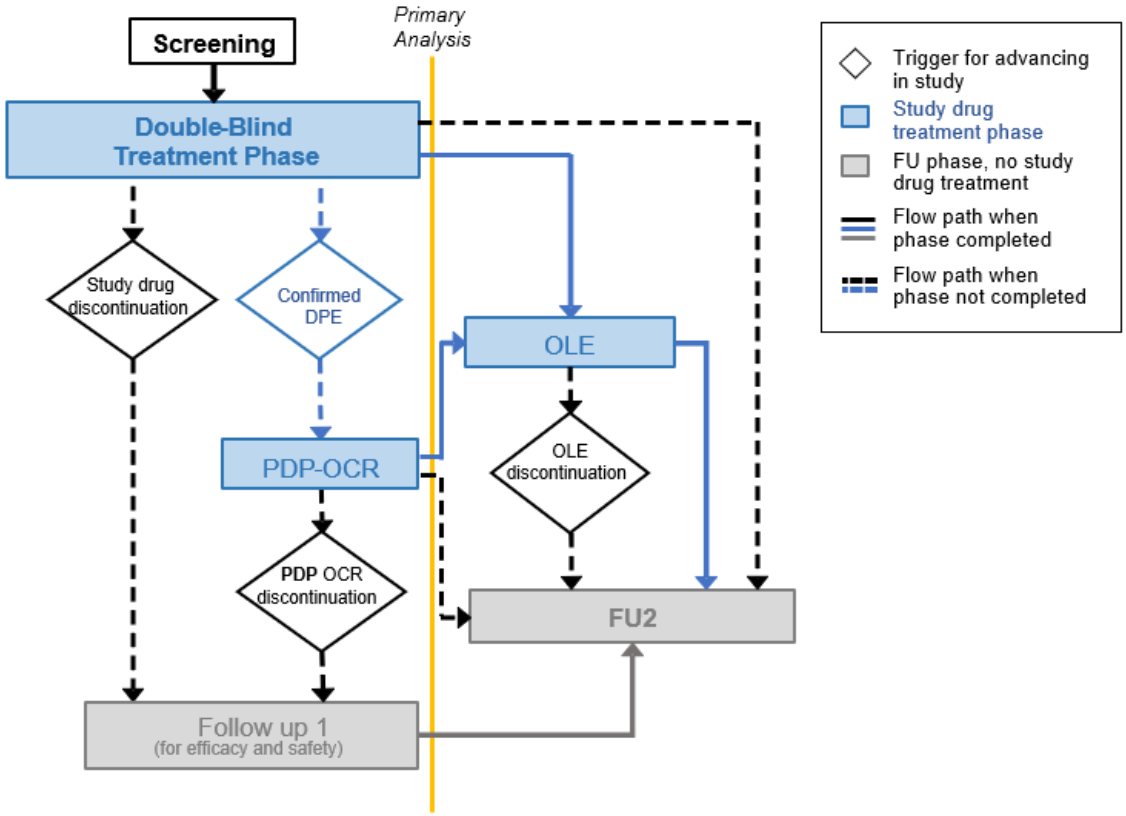
[a] Patients will be treated in the double-blind treatment phase for 144 weeks (6 study drug doses, with each dose 24 weeks apart) *or until the primary analysis, whichever occurs earlier.* Eligible patients *who either have completed* 144 weeks of double-blind treatment *or are ongoing in the* double-blind treatment phase at the *time of the primary analysis will switch to open-label treatment at the* next *scheduled* visit.

[b] Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to the PDP OCR phase after they completed at least 120 weeks of double-blind treatment and 120-week visit assessments (see Section 3.1.1.3 for definitions of DPE and PDP OCR). To maintain the blinding in the treatment arm, the first dose of PDP OCR treatment will be two infusions of 300 mg given 14 days apart for all patients. Subsequent doses will then be 600 mg IV infusions every 24 weeks. Patients who discontinue from the PDP OCR phase may continue to be followed in the FU2 phase.

[c] At the Week 144 visit, patients will complete the efficacy assessments in a blinded manner as part of the double-blind treatment phase and will receive open label ocrelizumab. *Each* patient will remain in the OLE phase for at least 2 years (at least 4 doses of ocrelizumab). To maintain the blinding in the treatment arm, the first dose of open-label treatment will be two infusions of 300 mg given 14 days apart for all patients. For subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks. Patients who discontinue from the OLE phase may continue to be followed in the FU2 phase.

[d] *The primary analysis will be performed after the last randomized patient reaches 144 weeks of double-blind treatment (+ 12 weeks to allow for the confirmation of the latest event) or when at least 340 events are reached, whichever occurs earlier.*

Figure 2 Patient Flow Schema



DPE = double-progression event; FU = follow up; OCR = ocrelizumab; OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab.

Notes: A patient may discontinue treatment and/or discontinue from the study at any time. Qualifications for advancing and the duration of each study phase are detailed in Section 3.1.1. The size of the boxes in this diagram does not represent the duration of each phase; for visit schedule and assessments required, see the schedule of activities for each phase.

Table 3 Overview of the Dosing Regimen across Study Phases

	Double-Blind Treatment Phase							PDP OCR			OLE Phase		
	6 Treatment Doses (144 Weeks) [a, b, c, d]							Variable [b, d, e]			At Least 4 Treatment Doses [b, d, f, g]		
	Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	Dose 6 [a, c] (Every 24 Wks)	PDP OCR Dose 1 [h]		PDP OCR Dose 2, 3, N	OLE Dose 1 [e, g] Double Infusion [g]		OLE Dose 2, N (Subsequent Treatment Doses) [g] (Every 24 Wks)
	Day 1	Day 15	Wk 24	Wk 48	Wk 72	Wk 96	Wk 120+	Day 1	Day 15	Day N	Day 1	Day 15	Day N
A OCR	300 mg	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg
B Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	OCR 300 mg	OCR 300 mg	OCR 600 mg	OCR 300 mg	OCR 300 mg	OCR 600 mg

9-HPT = 9-Hole Peg Test; CDP = confirmed disability progression; DPE = double-progression event; OCR = ocrelizumab; OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab; wk = week.

Note: Each study drug dose has a duration of 24 weeks (±5 days).

[a] The double-blind treatment phase consists of a 144-week (6 study drug doses, with each dose 24 weeks apart) period.

[b] After the first infusion, an evaluation will be performed before each subsequent infusion to ensure the patient remains eligible for further treatment (see also Section 4.3.2.3 for re-treatment criteria for ocrelizumab).

[c] Enrolled patients will undergo ocrelizumab (or placebo) treatment of 6 treatment doses at 24-week intervals.

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

[e] Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to the PDP OCR phase after they have completed at least 120 weeks of double-blind treatment. A DPE is defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks that occurs during the double-blind treatment phase.

[f] The OLE phase for eligible patients begins after the completion of the double-blind treatment phase *or at the time of primary analysis*. The OLE phase can be terminated at any point (see Section 3.1.1.5).

Table 3 Overview of the Dosing Regimen across Study Phases (cont.)

[g] During the OLE phase, the first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks. The first infusion of ocrelizumab in the OLE phase may occur once the patient meets the re-treatment criteria (see Section 4.3.2.3) at a scheduled visit following communication with the Sponsor.

[h] To maintain the original blinding, PDP OCR will be offered to all patients who qualify regardless of their original treatment assignment. Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to the PDP OCR phase after they have completed at least 120 weeks of double-blind treatment. The first dose of the PDP OCR will be administered as two 300 mg ocrelizumab infusions (given 14 days apart) 24 weeks after the last dose of blinded study drug.

3.1.1 Study Phases

This study will consist of the following study phases:

- Screening
- Double-blind treatment
- An optional PDP OCR treatment
- Follow-up 1
- Open-label extension
- Follow-up 2

The details of each study phase are described below and in Figure 1. The study duration will vary for each patient to maximize the safety and efficacy data collected.

3.1.1.1 Screening Phase

The screening phase will last up to 24 weeks. Patients who are candidates for enrollment in the study will be evaluated by the investigator to ensure all eligibility criteria are met (see Sections 4.1.1 and 4.1.2). All patients must sign the Informed Consent Form prior to screening and prior to any changes to their existing medication for the purposes of enrollment in the study.

Procedures at screening will include collecting medical history, medical examination, complete neurological examination, 9-HPT time and EDSS score, and blood and urine sampling (see Appendix 1 for further details on screening assessments and samples and Section 4.1 on eligibility criteria for the study). Because of the potentially long screening phase (up to 24 weeks), the investigator is required to verify that the patient still meets eligibility criteria prior to randomization. Patients must be neurologically stable for at least 30 days prior to randomization and baseline assessments. In particular, laboratory assessments related to eligibility should not be older than 6 weeks prior to randomization; otherwise, laboratory retests will be required (not applicable for CSF testing).

Two mandatory MRI scans performed at least 6 weeks apart or one mandatory MRI that can be compared with a historical MRI performed in the previous 1 year will be performed to verify the patient's MRI activity level. The MRI performed closer (i.e., from 6 weeks up to 10 days prior) to randomization will be considered the baseline MRI for the study analyses.

For patients who fail the initial screening, a maximum of two re-screenings will be allowed.

Central randomization will be performed by the IxRS and will be stratified by:

- MRI activity, defined as any T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) during the screening period (yes vs. no)

- Age (≤55. vs. >55)
- EDSS score (≤6.5 vs. >6.5)
- Region (two regions: European Union, United Kingdom, and Canada vs. other)

To ensure a balanced distribution of patients, demographics across regions by patient access to commercial ocrelizumab and enrollment within randomization strata will be monitored. Enrollment caps will be implemented in the IxRS system (e.g., no more than 650 patients will be randomized to the MRI-inactive subgroup). Other dynamic enrollment caps may be added to ensure that distribution of patients according to stratification factors will be balanced across regions by patient's access to commercial ocrelizumab.

Patient eligibility information will be provided by the investigator or the investigator's research staff to the IxRS at randomization. The patient will be randomized and assigned a unique medication number and randomization number.

Depending on local availability, patients who choose to and consent to the optional smartphone-based digital outcome assessments (Floodlight RPM) at screening will be asked to begin performing digital assessments (see Appendix 1). Screening for Floodlight RPM participation will close in November 2022 in order for the last Floodlight RPM patient enrollment to occur by the end of December 2022.

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

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

3.1.1.2 Double-Blind Treatment Phase

All patients will undergo 144 weeks of study treatment (see Table 3 for review of dosing regimen) *or until the primary analysis, whichever occurs earlier*. Study assessments will be performed as described in the schedule of activities (see Appendix 1). Randomization (Day 1) will occur only after the patient has met all inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2). Patients will be randomized to either ocrelizumab or placebo control group.

Study drug (ocrelizumab or placebo) dose will be administered in this study every 24 weeks. The first dose of study drug will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, study drug will be administered as a single 600 mg IV infusion every 24 weeks. All patients will receive mandatory premedication prior to each infusion. A minimum interval of 20 weeks should be kept between the ocrelizumab second infusion of Dose 1 (i.e., infusion Day 15) and the next infusion of Dose 2 (Week 24). A minimum interval of 22 weeks must be maintained

between each dose of study drug. More detailed information on study drug administration and premedication is contained in Section 4.3.2.1 and in Table 3.

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 may be administered within 48 hours of randomization provided the investigator ensures 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.

Patients who prematurely withdraw from study treatment during the double-blind treatment phase will remain blinded to treatment and will continue to be followed for safety and efficacy, regardless of switching to other medications for 144 weeks after randomization for each patient *(in the FU1 phase) or until the primary analysis.*

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind treatment phase as a result of adverse events or changes to laboratory results, several additional measures, including a "dual assessor approach" (i.e., two blinded investigators per site: Treating Investigator and Examining Investigator), will be implemented until the time of the primary analysis; see Section 4.2 for details and definitions.

The primary analysis will be performed after the last randomized patient reaches 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event) *or when at least 340 events are reached, whichever occurs earlier.*

3.1.1.3 An Optional Post-Double-Progression Ocrelizumab Treatment Phase

A double-progression event (DPE) is defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks. Patients who experience a DPE during the double-blind treatment phase will be notified by the Sponsor and given the option switch to ocrelizumab (PDP OCR) treatment after they have completed at least 120 weeks of double-blind treatment and 120-week visit assessments. Patients will have to provide his or her informed consent prior to switching to PDP OCR treatment. An iDMC will monitor the rate of DPE in the double-blind treatment period.

In order to maintain the original blind, the option for PDP OCR will be offered to all patients who qualify, regardless of their original treatment assignment. The first dose of the PDP OCR will be administered as two 300 mg IV infusions (given 14 days apart) 24 weeks after the last dose of study drug. Subsequent doses will be 600 mg IV infusions every 24 weeks. Patients may continue on PDP OCR treatment until the end of the OLE phase. Patients who discontinue from the PDP OCR phase earlier may continue to be followed in the FU2 phase.

3.1.1.4 Follow-Up 1 Phase

All patients who discontinue prematurely from the double-blind treatment phase will enter the FU1 phase, including patients who receive other DMTs for MS, commercial ocrelizumab, or no treatment. The FU1 phase will run in parallel with the double-blind treatment phase until 144 weeks from randomization for each patient *or until the primary analysis, whichever occurs earlier*. Scheduled visits will be performed every 12 weeks analogically to the initial (double-blind) schedule of activities and will include both efficacy and safety assessments (see Appendix 2). In the FU1 phase, patients will remain blinded to their original (randomized) treatment assignment. Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the FU1 phase. All patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient *or at the time of the primary analysis* will continue in the FU2 phase (see Section 3.1.1.6).

3.1.1.5 Optional Ocrelizumab Open-Label Extension Phase

An optional OLE phase is planned for eligible patients who have *either* completed *144 weeks of* the double-blind treatment phase *or are ongoing in the double-blind treatment phase at the time of the primary analysis* and, in the opinion of the investigator, could benefit from ocrelizumab treatment. Patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient *or at the time of the primary analysis* will continue in the FU2 phase and will not participate in the OLE phase.

The OLE phase will be carried out for at least 2 years (at least 4 doses of ocrelizumab) for each patient. The 2-year duration of the OLE phase serves to further evaluate long-term safety and efficacy of ocrelizumab treatment in patients with PPMS.

Patients will continue in the OLE phase or with PDP OCR treatment as per the schedule of activities (see Appendix 1 and Appendix 2) and Table 3.

All patients who do not participate in the OLE phase will enter the FU2 phase (see Section 3.1.1.6).

Eligible patients will need to provide consent for participation in the OLE phase. Patients who consent to participate in the OLE phase will be required to meet the eligibility criteria for OLE prior to infusion with ocrelizumab (see Section 4.1.3).

During the OLE phase, the first dose of ocrelizumab will be given as two 300 mg IV infusions given 14 days apart. For the subsequent OLE doses, patients will continue open-label treatment with a single infusion of 600 mg ocrelizumab IV every 24 weeks (see Appendix 3 and Section 4.3.2.1). A minimum 22-week interval between the last study ocrelizumab infusion in the double-blind treatment phase and the first OLE ocrelizumab infusion must be respected. The first infusion of ocrelizumab in the OLE phase may occur once the patient meets the re-treatment criteria (see Section 4.3.2.3)

at a scheduled visit. Refer to Section 4.2 for additional information about study unblinding.

Patients who complete or withdraw from the OLE phase will enter the FU2 phase (see Section 3.1.1.6). The Sponsor may decide to terminate the OLE at any time (see Section 4.7.3).

Study WA40404 will remain blinded until the primary analysis. The mechanisms necessary to ensure that the blinding of the Examining Investigator is maintained are not necessary after the primary analysis during the OLE phase. All required assessments during the OLE phase should occur as described in OLE schedule of activities (see Appendix 3). It is recommended that the same Examining Investigator continues to perform the assessments throughout the OLE phase as in the double-blind phase.

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

To verify re-treatment criteria for OLE infusion Dose 2 and subsequent doses, patients must attend a scheduled visit approximately 2 weeks prior to the infusion visit to have safety assessments performed as described in Appendix 3. In the event that an infusion is delayed, additional tests or assessments, such as routine safety laboratory tests, may be performed by the Treating Investigator as clinically indicated. At infusion visits, patients should remain in observation for at least 1 hour after the completion of the infusion.

Additional unscheduled visits for the assessment of potential disease progression or MS relapses, new neurological symptoms, or safety events may occur at any time. Assessments performed at unscheduled (non-dosing) visits will be as clinically indicated.

Patients with new neurological symptoms suggestive of MS relapse or MS worsening should have an EDSS and 9-HPT performed by the Examining Investigator (within 7 days from the onset of the new neurological symptoms). Other tests/assessments may be performed as appropriate.

3.1.1.6 Follow-Up 2 Phase

The following patients will move into the FU2 phase (see Figure 2):

- Patients who are ongoing in the FU1 phase at 144 weeks from randomization for each patient *or at the time of the primary analysis*

- Patients who have *either* completed 144 weeks of the double-blind treatment phase *or are ongoing in the double-blind treatment phase at the time of the primary analysis* and will not enter the OLE phase
- Patients who have completed or withdrawn from the OLE phase or from PDP OCR treatment phase

Laboratory and safety assessments for the FU2 phase will be performed during the clinic visit that occur 24 weeks *after the last visit either in double-blind treatment phase, OLE, PDP OCR or FU1, whichever phase the patient is at that time* (see Appendix 4). All patients will continue in the FU2 phase *for 24 weeks*.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study will occur when *the last patient completes the last scheduled visit at the end of the FU2 phase or discontinuation visit.*

The total length of the study, from screening of the first patient to the end of the study, is expected to be *up to 10.5 years* (assuming that the last patient randomized after *5 years* from the start of the study has received blinded treatment for 144 weeks, followed by OLE phase for at least 2 years (at least 4 doses of ocrelizumab) for each patient, *24 weeks* of FU2 phase) *(assuming that the number of 340 events has not been reached earlier).*

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

3.3 *DURATION OF PARTICIPATION*

The total duration of study participation for an individual is expected to be approximately up to 10.5 years.

3.4 RATIONALE FOR STUDY DESIGN

This study (WA40404) is a pivotal Phase III clinical trial composed of the following phases: screening, double-blind treatment, an optional PDP OCR treatment, FU1, OLE, *and* FU2. The double-blind treatment phase is designed to demonstrate the efficacy and safety of ocrelizumab in patients with PPMS, including those later in their disease course, in comparison with placebo. The OLE phase serves to further evaluate long-term safety, tolerability, and efficacy of ocrelizumab treatment in patients with PPMS.

3.4.1 Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg every 24 weeks.

Ocrelizumab will be administered intravenously as dual infusions (300 mg on Days 1 [Dose 1 Infusion 1] and 15 [Dose 1 Infusion 2]) for the first dose and subsequently as a single IV infusion (600 mg) every 24 weeks in 500 mL 0.9% sodium chloride. This dosing regimen is consistent with the dosing regimen used in ocrelizumab Phase III/IV

studies, as well as with the summary of product characteristics (SmPC) and the U.S. prescribing information (USPI).

In the double-blind treatment phase, study drug for patients randomized to the placebo group will be administered analogously to those receiving ocrelizumab.

3.4.2 Rationale for Patient Population

In comparison with the previous ocrelizumab PPMS study (WA25046), this study will evaluate the efficacy of ocrelizumab compared with placebo in a population that also includes patients with more advanced PPMS who acquired significant lower extremity impairment. This study will enroll patients with PPMS with an EDSS score of 3.0-8.0 and duration of disease less than 10 years if EDSS score $\leq$5.0 or less than 15 years if EDSS score 5.5–6.5 or less than 20 years if EDSS score 7.0–8.0 with an age range up to $\leq$65 years. These criteria will be implemented to recruit patients with PPMS later in their disease course and with a higher severity of disability. The study will *also* evaluate *the efficacy of ocrelizumab on the preservation of* upper limb function using the 9-HPT measure as a *key secondary* objective, and the treatment effect of ocrelizumab will be explored according to the presence of inflammatory activity on MRI at baseline.

3.4.3 Rationale for Control Group

In this study, the control group treatment is placebo.

PPMS is a neurologically disabling condition, without a disease-modifying treatment until recently. Ocrelizumab is the first and currently the only MS treatment approved for the PPMS indication, and its label differs depending on the region. Ocrelizumab was approved by the European Commission on 8 January 2018 for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Additional evidence was requested by the EMA Committee for Medicinal Products to further elaborate the effect of ocrelizumab on the patient population with PPMS later in their disease course (EDSS score $>$6.5), in patients aged 55–65 years, and in patients with different inflammatory profiles.

Pursuant to the Helsinki Declaration, when standard treatment of a disease exists, placebo should generally not be used in clinical trials (WMA 1964). The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

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

To better contextualize the efficacy of the various PPMS subgroups, a broader population needs to be investigated in a controlled trial. Given that no standard therapy exists in the European Union and some other parts of the world for the treatment of patients with PPMS later in their disease course/without imaging features characteristic of inflammatory activity, a placebo-controlled trial is acceptable provided that appropriate patient consent and safeguards are instituted to minimize the risk of serious or irreversible harm resulting from exposure to placebo. In this study, patients randomized to placebo who experience a DPE during the double-blind treatment phase will be given the option to switch to ocrelizumab (see Section 3.1.1.3).

The Sponsor recognizes that a treatment period lasting *up to* 144 weeks poses risks to patients randomized to placebo. For this reason, several study elements will be employed to protect the well-being of study participants:

- The Informed Consent Form clearly defines the duration of the study including the double-blind treatment phase, OLE phase, and follow-up phases. The probabilities of assignment to placebo and ocrelizumab are indicated in easily understood terms in multiple sections of the Informed Consent Form.
- Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment (see Section 3.1.1.3 for definition of DPE). Patients will have to provide their informed consent prior to switching to PDP OCR.
- A thorough medical monitoring plan will be implemented by the study Sponsor to ensure the safety of all study participants. Moreover, an iDMC will be instituted to further protect the wellbeing of patients in the study.
- Upon withdrawal from study treatment for any reason, patients will be recommended to stay in the study for follow-up but may be eligible for treatment with some alternative therapies at the discretion of and in consultation with their Treating Investigator.

3.4.4 Rationale for the Use of Premedications (Methylprednisolone and Antihistamines)

To reduce the frequency and severity of infusion-related reactions (IRRs), patients will be premedicated with 100 mg methylprednisolone IV *(or equivalent oral dose of prednisolone or methylprednisolone, should IV methylprednisolone not be available)* and an antihistamine approximately 30 minutes prior to administration of ocrelizumab (see Section 4.3.2.2). An integrated analysis of patients with MS who were treated with ocrelizumab revealed that the addition of antihistamines to the pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold (OCREVUS® U.S. Package Insert). Administered infrequently at a low dose, methylprednisolone is not anticipated to affect the efficacy or safety outcomes of the study. Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated) will be administered to patients in both treatment groups during the treatment period to maintain the treatment blind.

3.4.5 Rationale for Biomarker Assessments

A blood protein biomarker sample (plasma and serum) will be taken. Assessment of the sample may include, but will not be limited to, NfL, a marker of neuronal injury and/or other neurodegeneration/inflammatory markers. Biomarkers of neuroinflammation, including NfL, an acute neuronal injury marker, has been correlated with Gd-enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in PPMS and RMS (Gunnarsson et al. 2011; Axelsson et al. 2014, Kuhle et al. 2019). NfL can be detected in the blood, and blood levels are correlated with CSF levels, making NfL an attractive non-invasive biomarker to assess neuronal injury in MS (DiSanto et al. 2017). In addition, NfL is prognostic for worse disability outcome in RMS and PPMS (Bar-Or et al. 2019; Kuhle et al. 2019). If the patient requires a CSF sample to screen for IgG index or the presence of oligoclonal bands at screening, the leftover CSF will be stored and the assessment of the sample may include, but will not be limited to, NfL. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL. NfL, in addition to other possible markers, may be used to assess the patient's disease activity, and/or as a pharmacodynamic, prognostic, or predictive biomarker(s) for disease progression and/or to assess drug activity, efficacy, safety, or MS pathogenesis.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from exploratory safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.4.6 *Rationale for Collection of Information on Race and Ethnicity*

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of PPMS according to race or ethnicity.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1000 patients will be enrolled in this study, of which at least 350 patients are planned to be in the MRI-active subgroup.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent and be compliant with the study protocol
- Diagnosis of PPMS in accordance with the McDonald criteria (Thompson et al. 2017)
- Age 18–65 years at time of signing Informed Consent Form
- EDSS score at screening and baseline $\geq$ 3.0 to 8.0, inclusive
- Disease duration from the onset of MS symptoms relative to randomization date:

  Less than 20 years in patients with an EDSS score at screening 7.0–8.0

  Less than 15 years in patients with an EDSS score at screening 5.5–6.5

  Less than 10 years in patients with an EDSS score at screening $\leq$ 5.0
- Documented history or presence at screening of at least one of the following laboratory findings in a CSF specimen (source documentation of laboratory results and method must be verified)

  Elevated IgG index

  One or more IgG oligoclonal bands detected by isoelectric focusing
- Screening and baseline 9-HPT completed in $>$ 25 seconds (average of the two hands)
- Ability to complete the 9-HPT within 240 seconds with each hand at screening and baseline
- Neurological stability for $\geq$ 30 days prior to baseline
- Patients previously treated with immunosuppressants, immunomodulators, or other immunomodulatory therapies must undergo an appropriate washout period according to the local label of the immunosuppressant/immunomodulatory drug used

  Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy for non-medical reasons should specifically be informed before deciding to enter the study of their treatment options and, that by participating in this study, they may be randomized to placebo for a period of 120 weeks or greater.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the

treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

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

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For female patients without reproductive potential:

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

4.1.2 Exclusion Criteria

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

- History of relapsing-remitting or secondary progressive MS at screening

- Confirmed serious opportunistic infection including: active bacterial, viral, fungal, mycobacterial infection or other infection, including tuberculosis or atypical mycobacterial disease
- Patients who have or have had confirmed or a high degree of suspicion of progressive multifocal leukoencephalopathy (PML)
- Known active malignancy or are being actively monitored for recurrence of malignancy
- Immunocompromised state, defined as one or more of the following:

  CD4 count $< 250/\mu L$

  Absolute neutrophil count $< 1.5 \times 10^3/\mu L$

  Serum IgG < 4.6 g/L
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization
- Inability to complete an MRI (contraindications for MRI, including but not restricted to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.) or contraindication to Gd administration
- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization.
- Contraindications to mandatory premedications (i.e., corticosteroids and antihistamines) for IRRs, including:

  Uncontrolled psychosis for corticosteroids

  Closed-angle glaucoma for antihistamines
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study, including, but not limited to, the following:

  History of hemorrhagic or ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or hemorrhage or ischemia of the spinal cord

  History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)

  History of metabolic myelopathy or known presence of untreated causes of metabolic myelopathy (e.g., untreated vitamin B12 deficiency)

  History or known presence of infectious myelopathy (e.g., due to syphilis, Lyme disease, HTLV-1, herpes zoster)

  History of genetically inherited progressive CNS degenerative disorder (e.g., mitochondrial myopathy, encephalopathy, lactic acidosis, stroke [MELAS] syndrome, and hereditary paraparesis)

  Neuromyelitis optica

History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)

History or known presence of sarcoidosis

History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

- Pregnant or breastfeeding, or intending to become pregnant during the study and for 6 or 12 months (as applicable by the Ocrevus local label) after last infusion of the study drug
- Lack of peripheral venous access
- Significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine or gastrointestinal, or any other significant disease that may preclude patient from participating in the study
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History of alcohol or other drug abuse
- History of primary or secondary (non drug-related) immunodeficiency
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Previous treatment with B cell-targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab, and alemtuzumab)
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

  The screening period may be extended for patients who have used systemic corticosteroids for MS before screening. For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive serum β-hCG measured at screening or positive urine β-hCG at baseline
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA PCR)
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus®) local label, if more stringent than the above

- Lack of MRI activity at screening/baseline if more than 650 patients without MRI activity have already been enrolled, as defined by T1 Gd+ lesion(s) and/or new and/or enlarged T2 lesion(s) in the screening, to ensure that at least 350 patients with MRI activity will be randomized

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

4.1.3 Eligibility Criteria for Open-Label Extension Phase

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

- *Either* completed *144 weeks of* the double-blind treatment phase of the trial *or are ongoing in the double-blind treatment phase at the time of the primary analysis* and who, in the opinion of the investigator, may benefit from treatment with ocrelizumab

  Patients who withdrew from study treatment and received another disease-modifying therapy (DMT) or commercial ocrelizumab will not be allowed to enter in the OLE phase.

- Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraceptive methods during the treatment period and for 6 or 12 months (as applicable by the Ocrevus local label) after the final dose of ocrelizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

  Birth control methods that are highly effective (i.e. failure rate < 1% [CTFG]) may also be used but are not required, and include: (1) oral, intravaginal or

transdermal combined hormonal contraception associated with inhibition of ovulation; (2) oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; (3) intrauterine device; (4) intrauterine hormone-releasing system; (5) bilateral tubal occlusion; (6) vasectomised partner; (7) sexual abstinence.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

For female patients without reproductive potential:

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

4.2 METHODS OF TREATMENT ASSIGNMENT AND BLINDING

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. Eligible patients must be randomized through IxRS prior to receiving any study drug. Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study.

The randomization list will not be available to the study centers, monitors, project statisticians, or to the Sponsor project team. All individuals directly involved in the study will remain blinded to the treatment assignment until the primary analysis.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind treatment phase as a result of adverse events or changes to laboratory results, the following additional measures will be implemented until the time of the primary analysis:

- To prevent potential unblinding as a result of adverse events or laboratory changes, a **"dual assessor"** approach will be used to evaluate efficacy and safety**. Each site will have two blinded investigators: a principal or Treating Investigator and a rating or Examining Investigator.**

  The Treating Investigator will be the safety assessor and should be a neurologist with experience in the care of patients with MS. The Treating Investigator will have access to safety data only and will make all treatment decisions based on the patient's clinical response and laboratory findings.

The Examining Investigator will be the efficacy assessor and should be a neurologist or other qualified health care practitioner trained and certified in administering and scoring the 9-HPT, Functional System Scores (FSS) and EDSS, and SDMT. **The Examining Investigator (or her/his certified designee) will assess the 9-HPT, EDSS scores (including dysphagia/bladder dysfunction assessments), and SDMT**. Until the primary analysis, the Examining Investigator and their qualified designees (if applicable) will not be involved with any aspect of medical management of the patient and will not be allowed access to patient data.

The Treating Investigator and the Examining Investigator will not be allowed to switch roles. Until the primary analysis, an investigator/site staff at a single site may not be a treating investigator for some patients and an examining investigator for others.

- Patient education: During the double-blind treatment phase, prior to being examined by the Examining Investigator, patients should be instructed not to discuss with the Examining Investigator what (if any) adverse effects they may be experiencing.
- Blinded, central MRI assessments: During the double-blind treatment phase, a blinded, central MRI reader will assess all MRI scans performed during the study. Of note, screening and baseline scans will be used for the assessment of patient eligibility, and therefore they will not be blinded.
- Blinding of laboratory parameters: Selected laboratory parameters that may lead to unblinding of the treatment assignment, such as flow cytometry assessment of cell counts including CD19+ cells, lymphocyte count, and Ig levels will be blinded in all patients until the primary analysis. To ensure patient safety during the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and the Medical Monitor(s) with reflex messages triggered by abnormal blinded laboratory results and will be instructed to suspend further treatment with study drug until the patient becomes eligible for ocrelizumab re-treatment. Investigators will be notified of their patient's abnormal laboratory test results. Consult the laboratory manual for additional information.
- Ocrelizumab and placebo treatment allocation will remain blinded until the primary database lock for the primary analysis.

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

Study site personnel and patients will be blinded to treatment assignment until after the primary analysis. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the

unblinding group responsible, clinical supply chain managers, sample handling staff, IxRS service provider, and iDMC members.

While PK and ADA samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except at baseline or by request (e.g., to evaluate a possible error in dosing). ADA samples will be analyzed for all patients treated with study drug.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code *in an emergency situation. However, the Medical Monitor should be informed that the treatment code has been broken.*

The investigator will also be able to break the treatment code to determine the suitability of subsequent medical care for a patient. However, approval must be obtained from the Medical Monitor if the investigator wants to break the treatment code to determine patient's eligibility for a subsequent clinical trial testing investigational medicinal products or procedures. The investigator must contact the Medical Monitor prior to breaking the treatment code for any reason other than a medical emergency. The investigator should document and provide a justification for any non-emergency unblinding.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is ocrelizumab and matching placebo used to maintain the blind.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab and Placebo

Ocrelizumab will be supplied by the Sponsor in 15 cc Type I glass vials as a sterile, single-use solution for IV infusion and contains no preservatives. Each vial contains 300 mg of ocrelizumab, at a nominal fill volume of 10 mL. The drug product is formulated as 30 mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20. Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 micrometer or less). For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure, local prescribing information, and Drug Preparation Guidelines.

In this study, ocrelizumab-matching placebo will be supplied by the Sponsor. The placebo will have the same composition and configuration as the drug product but will not contain ocrelizumab. Ocrelizumab placebo solutions for IV administration will be prepared by dilution of the ocrelizumab placebo into infusion bags containing 0.9% sodium chloride, using an identical procedure as for the active product.

4.3.1.2 Non-Investigational/*Auxiliary* Medicinal Products

In this study, non-investigational/*Auxiliary* medicinal products will include premedication to the ocrelizumab infusion. The following premedication will be used:

- Mandatory methylprednisolone (or an equivalent)
- Mandatory antihistaminic drug (e.g., diphenhydramine)
- Recommended oral analgesic/antipyretic (e.g., acetaminophen 1 g)

Refer to Section 4.3.2.2 for further details on premedication administration.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Any dose modification should be noted on the Study Drug Administration Electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for treatment modification, interruption, or discontinuation for patients who experience adverse events are provided in Section 5.1.4.3.

4.3.2.1 Ocrelizumab and Placebo

The ocrelizumab dose administered will be 600 mg every 24 weeks. The first dose of ocrelizumab will be administered as two 300 mg IV infusions given 14 days apart. For the subsequent doses, ocrelizumab will be administered as a single 600-mg IV infusion every 24 weeks. A minimum interval of 20 weeks must be kept between the

ocrelizumab second infusion during the double-blind treatment phase (Dose 1) and the next infusion at double-blind treatment phase (Dose 2). A minimum interval of 22 weeks must be maintained between each dose of ocrelizumab. This dosing regimen is consistent with the dosing regimen used in the ocrelizumab Phase III/IV studies, as well as with the SmPC and the USPI (see Table 4).

Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they completed at least 120 weeks of double-blind treatment (see Section 3.1.1.3 for details). To maintain the original blind, PDP OCR will be offered to all patients who qualify, regardless of their original treatment assignment. The first dose of the PDP OCR will be administered as two 300 mg IV infusions (given 14 days apart) 24 weeks after the last dose of blinded study drug. A minimum interval of 20 weeks must be kept between the ocrelizumab second infusion during the PDP OCR (Dose 1) and the next infusion at PDP OCR (Dose 2). A minimum interval of 22 weeks must be maintained between each dose of ocrelizumab.

Patients who are eligible (see Section 3.1.1.5) and wish to enter the OLE phase will receive two 300 mg IV infusions given 14 days apart for the first OLE dose (OLE Dose 1). For subsequent doses, patients will continue open-label treatment with a single IV infusion of 600 mg ocrelizumab every 24 weeks (OLE Doses 2-N; see Appendix 3 for more details).

Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs. It is anticipated that the patient will need to stay at the hospital or clinical site for a full day at an infusion visit. Each ocrelizumab 300 mg dose should be administered as a slow IV infusion over approximately 2.5 hours. Each ocrelizumab 600 mg dose should be administered as a slow IV infusion over approximately 3.5 hours.

Table 4 Overview of Ocrelizumab or Placebo Dosing and Schedule

	Amount of Ocrelizumab (or Placebo) to Be Administered		Infusion Instructions
Initial dose (600 mg), divided into two infusions [a]	Infusion 1	300 mg IV in 250 mL 0.9% sodium chloride	• Initiate the infusion at a rate of 30 mL/hr for 30 minutes. • The rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr. • Each infusion should be given over approximately 2.5 hours.
	Infusion 2 (2 weeks later) [b]	300 mg IV in 250 mL 0.9% sodium chloride	
Subsequent doses (600 mg), [b] once every 24 weeks	Single infusion [b]	600 mg IV in 500 mL 0.9% sodium chloride	• Initiate the infusion at a rate of 40 mL/hr for 30 minutes. • The rate can be increased in 40 mL/hr increments every 30 minutes to a maximum of 200 mL/hr. • Each infusion should be given over approximately 3.5 hours.

[a] For patients who receive ocrelizumab at study start of the double-blind phase, start PDP OCR, or start OLE.

[b] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for re-treatment.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for infusion-related reactions.

Alternative Shorter Infusion of Subsequent 600 mg Ocrelizumab Doses

If patient 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 during any treatment phase. This does not apply for any initial dose (i.e., for patients who receive ocrelizumab at study start of the double-blind phase, start PDP OCR, or start OLE). The shorter infusion should be started at a rate of 100 mL/h. This should be escalated at the rates shown in Table 5.

Table 5 Alternative Shorter Infusions of Ocrelizumab 600 mg

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

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

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

Refer to Section 5.1.1.1 of this protocol and to current version of the IB for further details on the alternative shorter infusion option, including safety information.

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

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

4.3.2.2 Premedications

Methylprednisolone has been shown to decrease the incidence and the severity of infusion reactions. An integrated analysis of patients with MS treated with ocrelizumab revealed that the addition of antihistamines pretreatment with methylprednisolone decreased the incidence of IRRs by 2-fold.

To reduce potential IRRs, all patients must receive mandatory prophylactic treatment with 100 mg of methylprednisolone administered by slow IV infusion *(or equivalent oral dose of prednisolone or methylprednisolone, should IV methylprednisolone not be available)*, to be completed approximately 30 minutes before the start of each ocrelizumab (or placebo) infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion.

Additionally, a mandatory oral or IV antihistaminic drug (such as IV diphenhydramine 50 mg or an equivalent dose of an alternative) must be administered approximately 30–60 minutes prior to the start of each ocrelizumab (or placebo) infusion.

Analgesic/antipyretic such as acetaminophen/paracetamol (1 g) can also be considered.

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

4.3.2.3 Re-Treatment Criteria for Ocrelizumab

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

- Absence of severe allergic or anaphylactic reaction to a previous ocrelizumab infusion

- Absence of any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Absence of active infection
- ANC $\geq 1.5 \times 10^3/\mu L$
- CD4 cell count $\geq 250/\mu L$
- IgG ≥ 3.3 g/L
- Negative pregnancy test

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

If any of these are not met prior to re-dosing, further administration of ocrelizumab must be suspended until resolved or held indefinitely.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

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

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

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

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

Refer to the pharmacy manual and the effective ocrelizumab for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Ocrelizumab

Patients may be eligible to receive ocrelizumab as part of the OLE phase of this study, as described in Section 3.1.1.5.

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

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

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

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

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The patient has been treated with commercial ocrelizumab
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for PPMS
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for PPMS

- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country
- *The Roche IMP is no longer manufactured.*

In these situations, the investigator and primary care physician will transition the study participant to an alternative therapy in accordance with institutional or local guidelines.

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

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug or ongoing therapy (e.g., physiotherapy) to the study completion/discontinuation visit. All such medications and therapies (including their indication) should be reported to the investigator and recorded on the appropriate eCRF.

4.4.1 Treatment for Symptoms of Multiple Sclerosis

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

4.4.2 Treatment of Relapses

Patients who experience a relapse during study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted: 1 g/day IV methylprednisolone for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such patients should not discontinue the treatment solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal (see Section 4.7.1).

4.4.3 Prohibited Therapy and Alternative Treatment Post Ocrelizumab

The following therapies for MS are not permitted during the study treatment phase: B cell-targeted therapies (e.g., rituximab, atacicept, belimumab, or ofatumumab), natalizumab, fingolimod, siponimod, alemtuzumab, daclizumab, cladribine, teriflunomide,

dimethyl fumarate, interferons, glatiramer acetate, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation, IV Ig, plasmapheresis, other approved or investigational therapies for MS.

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

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

4.4.4 Immunizations

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

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette-Guerin, 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 during ocrelizumab treatment and for as long as the patient is B-cell depleted.

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

Of note: for seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Refer to the current version of the Ocrelizumab Investigator's Brochure for further guidance and updates on immunization.

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screen Failures

All patients must sign and date the most current Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form before any study specific assessments or procedures (including screening evaluations) are performed. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened and document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), general cancer risk factors, breast cancer-specific risk factors, reproductive status, smoking history and smoking status, will be recorded at baseline.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment and ongoing therapies (e.g., physiotherapy including its indication) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained, and any changes in medications and allergies should be recorded.

Any previous medications taken for the treatment of MS since disease onset, including their start and end dates, and medications taken for the symptoms of MS in the 3-month period prior to the baseline visit will be recorded at the baseline visit.

Demographic data will include age, sex, and self-reported race/ethnicity, if allowed per local regulations.

4.5.3 Physical Examinations

A complete physical examination performed at screening should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure while the patient is in a seated position, pulse rate, and temperature.

On the infusion days, blood pressure, pulse rate, and temperature should be taken within 45 minutes prior to the premedication (methylprednisolone) infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion, and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Blood pressure and pulse rate will be recorded on the appropriate eCRF. Temperature should be measured and recorded in patient's notes only. Clinically significant abnormalities should be recorded on the Adverse Event or Infusion-Related Reaction/Cytokine-Release Syndrome eCRF. In the event of an IRR or if clinically indicated, additional vital signs readings (e.g., blood pressure and pulse rate) should be taken during and post-infusion at the discretion of the investigator and should be recorded on a dedicated Vital Sign eCRF.

4.5.5 Neurological Examination

A neurological examination will be performed by the Treating Investigator at every planned visit. During an unscheduled visit, the neurological examination will be performed only if deemed necessary.

In the presence of newly identified or worsening neurological symptoms at any given time in the study, a neurological evaluation should be scheduled promptly and performed within 7 days of onset of the new or worsening neurological symptom(s).

Study investigators will screen patients for signs and symptoms of PML through evaluation of neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). A mandatory MRI scan and CSF analysis may be warranted to assist in the diagnosis of PML. Refer to Appendix 5 for guidance on the diagnosis of PML.

Patients with suspected PML, defined as a new or worsening neurological symptom that necessitates MRI and/or lumbar puncture and CSF analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing (see Appendix 5). The Medical Monitor should be contacted by email and should be immediately contacted by telephone.

A patient with confirmed PML should be withdrawn from treatment. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor (see also Section 5.1.1.2).

4.5.6 9-Hole Peg Test

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function (Goodkin et al. 1988; Fischer et al. 1999b). The test device consists of a container containing nine pegs and a wood or plastic block containing nine empty holes. The patient is to pick up each of the nine pegs one at a time and as quickly as possible place them in the nine holes. Once all the pegs are in the holes, the patient is to remove them again one at a time as quickly as possible and replace them into the container. The total time to complete the task is recorded. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand).

The 9-HPT will be administered by the Examining Investigator or a qualified designee at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

4.5.7 Assessment of Disability: Expanded Disability Status Scale

Disability in MS is commonly measured by the EDSS. EDSS will be administered by the Examining Investigator at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, Appendix 3 and Appendix 4). The EDSS will be assessed in all patients by the Examining Investigator at screening, baseline, and every 12 weeks (regularly scheduled visit) during the double-blind treatment and FU1 phases; every 24 weeks during the OLE phase; at any unscheduled visit; and at treatment discontinuation, end of observation, or withdrawal from follow-up visit. Additional EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.). All FSS and total EDSS scores will be captured electronically.

EDSS CDP is 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 and ≥ 0.5 point when the baseline score is > 5.5. Disability progression is considered confirmed when the increase in the EDSS score is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of the progression. A 24-week CDP requires that the increase in EDSS score be confirmed at least 24 weeks after the initial documentation of the progression.

The EDSS is based on a standard neurological examination, incorporating 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 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). Note that the following

items need not be scored: sexual dysfunction and fatigue and consequently should not contribute to the Cerebral FS score nor EDSS step.

4.5.8 Assessment of Relapse

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

All new or worsening neurological events compatible with MS representing a clinical relapse are to be reported in the appropriate eCRF. Patients with clinical relapses should be referred to the Examining Investigator who will assess the EDSS/FSS independently to allow confirmation as to whether or not the clinical relapse(s) meet the criteria for protocol defined relapse(s). EDSS should be performed within 7 days from the onset of the relapse.

For this study, a relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of least 30 days. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least one of the following:

- Half a step (0.5 point) on the EDSS
- 2 points on one of the selected FSS as listed below
- 1 point on two or more of the selected FSS as listed below

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: sexual dysfunction and fatigue.

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

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded in the eCRF.

4.5.9 Symbol Digit Modalities Test

The SDMT (Smith 1982) 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 recognized as being particularly sensitive to slowed processing of information that is commonly seen in MS (Benedict et al. 2017). The SDMT is brief, is 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 will be collected orally, and administration time is approximately 5 minutes.

SDMT will be administered by the Examining Investigator or a qualified designee at the timepoints indicated in the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

4.5.10 Mandatory and Optional MRI Sequences

MRI will be used to monitor CNS lesions in patients with MS and potentially other pathophysiology, such as inflammation and neurodegeneration. Mandatory MRI scans (formally known as 'brain MRI') will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

During the screening phase, two mandatory MRI scans (performed at least 6 weeks apart, but not more than 24 weeks apart) or one MRI with the mandatory sequences that can be compared with a historical MRI acquired in the previous 1 year will be performed to assess the patient's MRI activity level. MRI activity is defined as the presence of any T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) during the screening period (see also Section 3.1). If the presence of new or enlarging lesions is ascertained, the patient will be stratified to the MRI-active subgroup. The MRI performed closer to randomization (i.e., either the second MRI scan at screening or the [only] screening MRI scan in the case where a historical scan was used for the assessment of MRI activity) will be considered as baseline MRI for the study analyses and will be captured under the baseline visit in the eCRF. Note that this baseline scan should be obtained maximum 6 weeks before but at least 10 days prior to performing the baseline visit to allow time for the centralized reading center to assess its quality and for potential re-scans if needed.

Postbaseline, the mandatory MRI scans will be obtained in all patients at Weeks 24, 48, and 72. From Week 72 onward, MRI scans will be performed every 48 weeks (i.e., at Week 120, 168, etc.). In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at withdrawal visit) if one was not performed during the prior 4 weeks. Mandatory MRI scans should occur within a window of ±4 weeks of the scheduled visit, as per the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4). At the Week 120 visit for patients switching to PDP OCR treatment, mandatory MRI scans should be obtained within 4 weeks before the Week 120 visit.

The mandatory MRI sequences are comprised of both brain and axial cervical spinal sequences if site technology is available, and data from these scans will contribute measurements for the key MRI secondary endpoints as well as novel exploratory

endpoints. For details of the mandatory MRI sequences, refer to the MRI Acquisition Procedures Manuals. Axial cervical spine sequences are not required for the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used for screening (if applicable), but these axial cervical spine sequences should be included in second mandatory MRI scan (considered the baseline MRI).

If site technology is available, in addition to the mandatory MRI sequences, optional, additional sagittal cervical spinal cord MRI sequences may be acquired for baseline, Weeks 24 and 120, at treatment discontinuation, and every 48 weeks in the OLE (according to the yearly schedule as carried over from the double-blind treatment phase). These sagittal cervical spine sequences provide further information on cervical spinal cord lesions and atrophy. Additional optional sagittal cervical spinal cord MRI sequences are not required to accompany the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used at screening, but these sequences should be included in the second mandatory MRI (considered the baseline MRI) scan. Subjects who choose to participate, an additional signed Informed Consent Form (ICF – denoted as 'Consent for optional cervical spinal cord MRI scans' in the master ICF), dedicated to the sagittal cervical spine is required. For details of the additional optional sagittal cervical spine MRI sequences, refer to the MRI Acquisition Procedures Manuals.

During the OLE, MRI mandatory and additional optional sagittal cervical spinal cord scans will be performed every 48 weeks (according to the yearly schedule as carried over from the double-blind treatment phase).

MRI assessments will include, but may not be limited to, T1-weighted scans before and after injection of Gd contrast, fluid-attenuated inversion recovery, proton density-weighted, and T2-weighted scans.

MRI scans will be read by a centralized reading center for efficacy endpoints. The centralized reading center will be blinded to treatment assignment, and the reading will be 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 will be described in a separate MRI Acquisition Procedures Manual.

All MRI scans will also be reviewed locally by a radiologist for safety, and the MRI scan report containing only non-MS pathology will be provided to the Treating Investigator. During the double-blind treatment phase, only the local radiologist/technician at the investigational site who is assigned to this study may have access to the MRI scans, except at screening and baseline when the Treating Investigator may view the MRI scan. To protect the blind, the Treating Investigator must not review the MRI scans (including additional optional cervical MRIs) obtained after randomization unless a safety concern

arises. In the event that the Treating Investigator becomes aware of these MRI results, this should be documented in the eCRF, indicating the reason.

Note: the treating investigator may have access to MRI scans performed during the OLE phase after the primary analysis.

If patients receive corticosteroids for an MS relapse, every effort should be made to obtain an MRI scan prior to the first corticosteroid dose if the pre-corticosteroid scan is within 1 week of the scheduled visit. In patients receiving corticosteroids for an MS relapse, there should be an interval of 3 weeks between the last dose of corticosteroids and the MRI scan.

4.5.11 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the central laboratory for analysis unless otherwise indicated (further details will be provided in the laboratory manual).

- Hematology: hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count
- Blood chemistry: AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, sodium
- Flow cytometry: Analysis will include, but is not limited to, the determination of the duration of B-cell depletion and recovery (CD19+), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts and/or other populations), and T-cell counts (CD3+, CD4+, CD8+).
- Quantitative Ig: Ig levels (IgG, IgM, and IgA)

ADA: Serum samples will be collected for determination of antibodies against ocrelizumab. Because ocrelizumab concentrations affect the ADA assay, the concentration of ocrelizumab will be measured as well at all timepoints with ADA assessment to enable interpretation of the results. Refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for details.

- Urinalysis**:** A urine dipstick will be performed at the site (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test at screening.

All women of childbearing potential must have regular pregnancy tests. A urine pregnancy test (sensitivity of at least 25 mU/mL β-hCG) will be performed locally at the timepoints shown in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. 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 study drug. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed by the central laboratory.

- Viral serology and detection: All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by PCR must be negative to be eligible.

  For patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 12 weeks during the double-blind phase. Retests will continue in OLE phase on a 24-week basis as per the scheduled visits. Patients in whom the viral DNA becomes positive but in whom the quantity is at the lower limit of detection of the assay should have the test repeated as soon as possible. Patients found to have a confirmed viral DNA-positive test should be referred to a hepatologist for immediate assessment. These patients will not receive further infusions of study drug and will enter the follow-up phase.

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

- Biomarker sample: A plasma and a serum sample will be collected, and analysis may include, but will not be limited to, NfL. The sample may be shipped to the Sponsor, or one or more laboratories designated by the Sponsor for analysis.
- CSF: If the patient does not have documented history or presence at screening of at least one laboratory finding of either elevated IgG index or one or more IgG oligoclonal bands detected by isoelectric focusing on a prior CSF specimen, a CSF specimen will be collected to test for these parameters during the screening phase. The remainder of this CSF sample will be retained as a biomarker sample, and analysis may include, but will not be limited to, NfL. The sample may be shipped to the Sponsor, or one or more laboratories designated by the Sponsor for these analyses. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL.

All laboratory samples collected during the study will be shipped to a central laboratory, with the exception of urine dipsticks/urine probes, which will be analyzed locally unless otherwise indicated.

Laboratory samples will be taken at the study visit as described in the schedules of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

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

At participating sites, screening blood and CSF samples collected from patients who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and/or serum samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed
- Any leftover CSF samples that were collected for IgG index/OCB analysis to determine eligibility for patients who did not have historical data and the optional Week 48 CSF sample will be destroyed no later than 5 years after the final Clinical Study Report has been completed or until exhausted, or earlier depending on local regulations.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data, unless more stringent local requirements apply.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.12 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected via questionnaires to characterize the treatment benefit of ocrelizumab. The questionnaires, translated and culturally validated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

In the event that the patient is unable to complete PROs on his or her own (e.g., due to problems with eyesight or dexterity), appropriate site personnel (except the Examining Investigator) may administer the PRO to the patient; however, staff should not influence responses in any way and questions and response options should be read out verbatim.

Patients will use an electronic device to capture PRO data. The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

4.5.12.1 EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state (see Appendix 6). Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 5 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

4.5.12.2 Multiple Sclerosis Impact Scale, Version 2

The MSIS, v2 is a 29-item patient-reported measure of the physical and psychological impacts of MS (Hobart et al. 2001). Patients are asked to rate how much their functioning and well-being has been impacted over the past 14 days on a 4-point scale, from “Not at all” (1) to “Extremely” (4) (see Appendix 7). The physical score is the sum of items 1–20, which is then transformed onto a 0–100 scale. The psychological score is the sum of items 21–29, transformed onto a 0–100 scale. Higher scores indicate a greater impact of MS. A change of 7.5 points on the physical scale is considered to be clinically meaningful.

4.5.12.3 Modified Fatigue Impact Scale

The MFIS is a 21-item instrument that asks patients to rate the impact of fatigue over the past 4 weeks on a 5-point Likert scale, from “Never” (0) to “Almost always” (4) (Fischer et al. 1999a) (see Appendix 8). The total score is the sum of all items from 0 to 84, with higher scores indicating greater impacts of fatigue. Physical, cognitive, and psychosocial domain scores can also be calculated.

4.5.12.4 ABILHAND

The ABILHAND measures the ability to measure everyday activities that use upper limbs. It was originally developed for rheumatoid arthritis (Penta et al. 1998) and has since been used in MS (Cano et al. 2015; Mikol et al. 2015; see Appendix 9). Each item is scored on a 4-point scale, using "Impossible" (0), "Very Difficult" (1), "Difficult" (2), and "Easy" (3).

4.5.12.5 Quality of Life in Neurological Disorders Upper Extremity Function

The Neuro-QoL-UE (fine motor, activities of daily living [ADL]) domain is a 20-item questionnaire used to assess upper limb function, which involves people with MS

through each stage of its development (Gershon et al. 2012; see Appendix 10). Items include assessments of dressing, cooking, eating, cleaning, and writing from which the patient uses a 5-point Likert scale to rate his or her performance ranging from “without any difficulty” (5) to “unable to do” (1). Item scores are summed, multiplied by 100, and divided by 80; a higher score (range: 0−100) indicates better health reported function.

4.5.12.6 Patient Global Impression of Change for Fatigue

The Patient Global Impression of Change for Fatigue is a single item completed by the patient to assess changes in fatigue over the last 6 months (see Appendix 11). Patients will be asked to respond on a 7-point Likert scale from “very much better” (1) to “very much worse” (7).

4.5.12.7 Patient Global Impression of Change for Upper Limb Function

The PGIC-UL is a single item questionnaire completed by the patient to assess upper limb function compared with the function over the last 6 months (see Appendix 12). The patient will be asked to rate their upper limb function using a 7-point Likert scale ranging from “very much better” (1) to “very much worse” (7). The PGIC-UL is used as an anchor to determine what is a clinically meaningful change in ABILHAND and the Neuro-QoL-UE.

4.5.13 Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or other genotype analysis to assess the patient’s germline genotype for allelic variations or mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

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

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

Candidate genes of MS susceptibility or progression that have been identified will be assessed in DNA from the study patients and may include, but will not be limited to,

those in the human leukocyte antigen locus (IMSGC and WTCCC 2011; IMSGC 2013; Patsopoulos et al. 2013; Didonna and Oksenberg 2015). The genotype will also be assessed to identify potential new markers that may be prognostic of MS progression or disease worsening or to assess predictive value of markers for enhanced ocrelizumab response. The DNA genotype may be assessed for genes that have been associated with increased risk for MS or otherwise used to further understand the pathogenesis of MS (IMSGC and WTCCC 2011; IMSGC 2013).

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

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

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

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

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

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

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

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

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14) will not be applicable at that site.

4.5.14.3 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 or diseases:

- A single sample for DNA collected as indicated in the schedule of activities
- Plasma samples collected over time as indicated in the schedule of activities
- RNA samples collected over time as indicated in the schedule of activities
- Leftover samples from the main trial

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

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

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

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

4.5.14.4 Confidentiality

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

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

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

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

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

4.5.14.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.14.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. 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 patient 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 patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF.

If a patient 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 emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study WA40404 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WA40404.

4.5.14.7 Monitoring and Oversight

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

4.5.15 Optional Smartphone-Based Digital Outcome Assessment

Floodlight RPM digital outcome data collection encompasses active tests that have been developed to be self-administered by patients via smartphone devices. The Floodlight RPM assessment in this study may include, but may not be limited to, the following tests: information processing speed test; active gait and posture tests (only for patients with a baseline EDSS score $<$ 7.0), including a static balance test, a U-turn test, and a 2-minute walk test; hand motor function tests, including the "Draw a Shape" and "Pinching" test; daily mood questions; a MS symptom tracker; and the continuous analysis of mobility through passive monitoring. Patient participation in this data collection is optional. Only patients, who consent to Floodlight RPM self-assessments at screening will be asked to begin performing the digital assessment. The patient

adherence data from the 4 weeks prior to baseline will be used to determine if the patient can continue to use Floodlight RPM for 144 weeks from randomization *or until the primary analysis, whichever occurs earlier*. Screening for Floodlight RPM participation will close in November 2022 in order for the last Floodlight RPM patient enrollment to occur by the end of December 2022.

4.5.16 Optional CSF Collection

Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48 of the double-blind treatment phase; this sample will be used for exploratory biomarker determination that may include, but may not be limited to, NfL (see Section 3.4.5). The CSF sample should be collected prior to the ocrelizumab (or placebo) infusion at Week 48 (within a window of 14 days prior to the actual scheduled visit Week 48; see Appendix 1).

4.6 OVERVIEW OF CLINICAL VISITS

After the screening, patients who fulfill the entry criteria will be scheduled for baseline assessments. Visits will take place as described in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

Visits should be scheduled with reference to the date of the baseline visit (Day 1). A minimum interval of 20 or 22 weeks, depending if the previous dose was administered in one or two infusions as per Section 3.1.1.2, Section 3.1.1.3, and Section 3.1.1.5, respectively, should be maintained between each infusion.

At infusion visits, it is anticipated that the patients will have to stay at the hospital or clinic for a full day. Patients treated with ocrelizumab should remain in observation for at least 1 hour after the completion of the infusion. If for logistical reasons the infusion cannot be administered on the same study visit day, the infusion should be given within the next 24 hours provided that the patient still meets re-treatment criteria.

Patients who cannot receive their infusion at the scheduled visit or within 24 hours of the visit should be rescheduled for a delayed dosing visit (see Section 4.6.1). Additional unscheduled visits for the assessment of disease worsening, new neurological symptoms, or safety events may occur at any time.

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

4.6.1 Delayed Dosing Visit

Delayed dosing visits may be scheduled only if the infusion cannot be administered at the timepoints defined in the schedules of activities (see Appendix 1, Appendix 2,

Appendix 3, and Appendix 4). Thus, a patient who had all assessments of a dosing visit performed, but could not receive the infusion, should be rescheduled for the infusion on another day. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated.

4.6.2 Unscheduled Visits

Patients 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 and regardless of the study period. The EDSS assessment should be performed for any suspected neurological worsening. If an MS relapse is diagnosed or suspected, EDSS assessment should be performed within 7 days, in addition to completing the appropriate eCRF.

Other assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. The primary reason for performing an unscheduled visit will be reported in the eCRF.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator determines it is in the best interest of the patient

Additionally, patients must be withdrawn from treatment under the following circumstances:

- Life-threatening (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Demonstrate active hepatitis B infection, either new onset or reactivation
- PML
- Patients who decide to discontinue the treatment

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

An excessive rate of treatment withdrawals can render the study non-interpretable; therefore, unnecessary treatment withdrawal of patients should be avoided.

If a patient meets any of the treatment withdrawal criteria (see above), the patient must be withdrawn from treatment. Patients who prematurely withdraw from study drug treatment will need to return to the clinic for a treatment discontinuation visit (see Appendix 1, Appendix 2, and Appendix 3 for additional details). After treatment discontinuation, every effort should be made to have the patient enter the follow-up phase of the study (FU1 or FU2).

For patients who have withdrawn from study drug treatment, the investigator should decide as to further treatment of the underlying disease (see Section 4.4.3 for recommendations on alternative treatments for MS post-ocrelizumab).

4.7.2 Patient Discontinuation from Study

Patients will return to the clinic for an end of observation or withdrawal from follow-up visit.

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

- Patient withdrawal of consent
- Study termination or site closure

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients who withdraw from study drug treatment during any study period, for any reason, are encouraged to enter and complete the applicable follow-up phase (see Section 4.7.1). Patients who withdraw from FU1 or FU2 will return to the clinic for a withdrawal from follow-up visit (see Appendix 2 and Appendix 4 for additional details). If a patient discontinues from the study, the patient should be asked if he or she can still be contacted for further information, unless otherwise specified by the local requirements. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient withdrew from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated at the medical discretion of the investigator without their

consent. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

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

4.7.3 Study Discontinuation

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

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

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

4.7.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ocrelizumab in completed and ongoing studies. The anticipated important safety risks for ocrelizumab are outlined below. Refer to the ocrelizumab local labels and the Ocrelizumab Investigator's Brochure for a complete summary of safety information.

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

5.1.1 Risks Associated with Ocrelizumab

Important, identified, and potential risks associated with ocrelizumab are described in the approved risk management plan and provided below. Refer to the most recent version of the Ocrelizumab Investigator's Brochure for updates on risks associated with ocrelizumab treatment.

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions

All CD20-depleting agents administered via the intravenous route, including ocrelizumab, have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to the following: pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis.

Patients should be observed for at least 1 hour after the completion of the infusion for any symptom of IRR. Patients will be informed about delayed post-infusion symptoms and instructed to contact the study physician if he or she develops such symptoms.

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

For further guidance on how to manage IRRs refer to the current Ocrelizumab Investigator's Brochure.

Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143, ENSEMBLE Plus) designed to characterize the safety profile of shorter ocrelizumab infusions in patients with RRMS, no differences were found in the frequency and severity of IRRs associated with shorter (2 hour) infusions compared with conventional infusions (3.5 hours). For further details, refer to the current version of the Investigator's Brochure.

Infections

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

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

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

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

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

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

For PML, see Section 5.1.1.2 below.

Impaired Response to Vaccination

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

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

Investigators should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients who are on ocrelizumab. Vaccination with live or

live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

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

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

Decrease in Immunoglobulins

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

Serious Infections Related to Decrease in Immunoglobulins (Patients Previously Exposed to Immunosuppressive/Immunomodulatory Drugs or with Preexisting Hypogammaglobulinemia)

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

Delayed Return of Peripheral B Cells

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

5.1.1.2 Potential Risks

Malignancies (including Breast Cancer)

An increased risk of malignancy with ocrelizumab may exist. In controlled trials in MS, malignancies, including breast cancer, occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none

of 668 females treated with interferon β-1A or placebo. Patients should follow standard breast cancer screening guidelines.

Refer to the current Ocrelizumab Investigator's Brochure for more details.

If a malignant event is reported, key available information on cancer will be collected for this study and reported as a serious adverse event on the eCRF. Further explorations and detailed cancer information will be solicited via a questionnaire (e.g., further details on tumor diagnostics, grade/staging, and available histopathologic and genetic testing results).

Progressive Multifocal Leukoencephalopathy

John Cunningham (JC) virus infection resulting in PML has been reported very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors such as patient population or polytherapy with immunosuppressants. The reporting rate with ocrelizumab has been approximately 1 case per 100,000 patients. Since the risk of PML cannot be ruled out, 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 scans preferably with contrast (compared with pretreatment MRI scans), confirmatory CSF testing for JC viral DNA, and repeat neurological assessments should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently.

Refer to Appendix 5 for diagnosis guidance of PML. See the Ocrelizumab Investigator's Brochure for more details.

Hypersensitivity Reactions

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

Neutropenia

During the controlled treatment period, decreased neutrophils were observed in 12% and 15% of MS patients treated with ocrelizumab in PPMS and RMS, respectively. Most were mild to moderate in severity, approximately 1% of the patients had Grade 3 or 4 neutropenia; and no temporal association with infections was identified. On the basis of additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed. Refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.2 Risks Associated with Corticosteroids

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

5.1.3 Risks Associated with Antihistamines

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

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modifications

Study drug dose modifications are not foreseen.

5.1.4.2 Treatment Interruption

Study drug treatment may be temporarily suspended in patients who experience relevant adverse events considered to be related to study drug and prevent the patient from re-treatment with the study drug (see Section 4.3.2.3 for details on re-treatment criteria).

For female patients who become pregnant during the study, study drug treatment must be withheld for the duration of the pregnancy and breastfeeding. Study drug may be restarted following the delivery/end of breastfeeding, after discussing the risks and benefits of continuing the treatment (see Section 5.4.3).

5.1.4.3 Management Guidelines

Infusion-Related Reactions

Slowing of the infusion rate or interruption of the infusion may be necessary in the event of an infusion reaction. In rare cases, ocrelizumab treatment may need to be discontinued. Follow ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms (see also Table 6 for grading of intensity of IRRs).

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

For a **severe infusion-related event (Grade 3)** or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive aggressive symptomatic treatment. The infusion should be restarted 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.

For a **life-threatening infusion-related event (Grade 4**) during an infusion, the infusion should be immediately stopped, and the patient should receive appropriate treatment (including use of resuscitation medications and equipment that must be available and used as clinically indicated). The patient will be withdrawn from treatment and should enter the follow-up phase.

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion but not the total dose.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Clinical relapses will be recorded only on the appropriate eCRF. IRRs will be recorded only on a pre-specified Infusion-Related Reaction/Cytokine-Release Syndrome eCRF.

B-cell depletion is the expected outcome of ocrelizumab treatment and is not an adverse event. However, patients 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 patients reporting signs or symptoms of infection, to take appropriate specimens for identification of the pathogen, and to treat infections aggressively. Prior to enrollment in the study, it is recommended that the investigator review and, if warranted, update each patient's immunizations in accordance with country medical immunization guidelines (see Section 4.4.4).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

The exception to this definition of a serious adverse event is in the rare event that a patient is hospitalized following an MS relapse and the reason for hospitalization is to receive standard treatment with IV methylprednisolone. The rationale for this exception is that some countries and/or clinical sites routinely hospitalize patients who require administration of methylprednisolone in the event of an MS relapse. Thus, the serious adverse event criteria for "hospitalization" would be met on the basis of local practice and would not reflect the seriousness of the event.

If the MS relapse results in hospitalization for any reason other than for routine treatment of the relapse (e.g., for a treatment course beyond the standard treatment; see Section 5.3.5.11) or when hospitalization is prolonged, the MS relapse should be considered a serious adverse event.

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

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

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

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4.1–5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported throughout the study duration.

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

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

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

Table 7 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., “infusion-related reaction”) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction/Cytokine-Release Syndrome eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction/Cytokine-Release Syndrome eCRF. Report a local IRR for any symptoms affecting only the skin and localized to only one place.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of MS, "multiple sclerosis progression" should be recorded on the Adverse Event eCRF.

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of MS

Events that are clearly consistent with expected pattern of progression of the underlying disease should not be recorded as adverse events; however, clinical MS relapses will be recorded on eCRF. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on EDSS scores and/or 9-HPT times. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Occasional isolated symptoms that according to the investigator are caused by MS, but do not constitute a full MS relapse, should be reported as an adverse event, with the causality “Disease under study" (see Section 5.3.4).

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Elective hospitalizations or surgical procedures that are a result of a patient’s preexisting condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones and diagnostic testing. Such events should still be recorded as medical procedures in the eCRF.
- Hospitalization to receive study medication, such as infusions of ocrelizumab unless this is prolonged.
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone.

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

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

5.3.5.12 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Accidental overdoses or medication errors see Section 5.4.4 for details on reporting requirements)

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. To ensure the

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus.

Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. Information regarding child health up to 1 year should be collected on the infant health questionnaire (see Appendix 13).

5.4.3.2 Abortions

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

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

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

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

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

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

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

seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For ocrelizumab or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed with a Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire provided by the Sponsor.

5.5.2 Sponsor Follow-Up

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

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.

All adverse events must be collected and reported during the study through the end of the FU2 phase.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

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

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events *through the use of the reference safety information in the* Ocrelizumab Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

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

An iDMC will monitor the incidence of the above-listed anticipated events until primary analysis is performed. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan, which will be finalized prior to the *database* lock and unblinding of the study database. *The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The analyses specified in the SAP supersede those specified here.*

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo on *the composite 12-week CDP of EDSS and 9-HPT* in all randomized patients and in patients with MRI activity. The sample size was estimated on the basis of data from Study WA25046 (ORATORIO).

A two-group test of equal exponential survival is used to determine the sample size for the *composite 12-week CDP of EDSS and 9-HPT.* With a sample size of 1000 patients (of which at least 350 patients are expected in the MRI-active population), a double-blind treatment phase of 144 weeks, an annual dropout rate of 10%, and a randomization ratio of 1:1, it is expected that approximately *340* events will be observed in all randomized patients (placebo progression rate: 40%), which will provide approximately *80%* power to detect a hazard ratio of 0.70 at a type I error rate of 0.0146 and approximately *75.5%* power to detect a hazard ratio of 0.75 at a type I error rate of 0.05. Likewise, it is expected that approximately *122* events will be observed in the MRI-active subgroup (placebo progression rate: 44%), which will provide approximately *78%* power to detect a hazard ratio of 0.60 at a type I error rate of 0.04.

Operating characteristics (power and expected total number of events) for true underlying hazard ratio values of 0.60, *0.70*, and 0.75 are provided in Table 8 for all randomized patients and the MRI-active subgroup.

Table 8 Operating Characteristics for Possible True Underlying Hazard Ratio Values

	MRI-Active Subgroup	All Patients Randomized	All Patients Randomized
Expected number of events	*122*	*340*	*340*
Expected proportion of placebo patients with *composite events* at Week 120	44%	40%	40%
2-sided alpha for the log-rank test	0.04	0.0146	0.05
Power	*78%*	*80%*	*75.5%*
Detectable hazard ratio	0.60	0.70	0.75

MRI = magnetic resonance imaging.

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, and patients are followed for 144 weeks.

It should be noted that the type I error rate to be used for the testing in all randomized patients will be adjusted depending of the proportion of events in the MRI-active subgroup (see Section 6.4.1.3 for control of type I error).

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue treatment or study, or complete the study will be summarized. Reasons for premature treatment and study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, history of MS, stratification factors) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group, for the MRI-active subgroup and all randomized patients as allocated.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all randomized patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Analysis

The primary analysis will compare the time *to onset of composite 12-week CDP* between ocrelizumab and placebo in all randomized patients and in the MRI-active subgroup.

If at least one of the two co-primary analyses is statistically significant, then the trial is considered positive. Type I error will be controlled using a fallback and loop-back procedure (see Section 6.4.1.3).

There are two co-primary analyses:

- In all randomized patients
- In the MRI-active subgroup

The MRI-active subgroup is defined as patients with any T1 Gd lesion and/or new and/or enlarging T2 lesion during the screening period or at baseline.

Time to onset of composite 12-week CDP is defined as the time from randomization to the first occurrence of at least one of the following progression events:

- *12-week CDP in 9-HPT, defined as a worsening of 20% from baseline in 9-HPT confirmed for at least 12 weeks*
- *12-week CDP in EDSS, defined as an increase of ≥1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤5.5 or an increase of ≥0.5 point in patients with a baseline EDSS score of <5.5 that is confirmed for at least 12 weeks*

The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). The most recent EDSS measured before first dose administration (or randomization for non-treated patients) will be considered as baseline EDSS.

The 9-HPT time is the reciprocal of the score for the 9-HPT as described in the MS functional composite guide (National Multiple Sclerosis Society 2001). The score for the 9-HPT is an average of the four trials (2 for the dominant hand and 2 for the non-dominant hand), calculated as follows: the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand, and then the two reciprocals are averaged. The most recent 9-HPT measured before first dose administration (or randomization for non-treated patients) will be considered *as* baseline *9-HPT.*

In each component (EDSS and 9-HPT), CDP is considered confirmed when the increase is sustained at the next regularly scheduled visit at least 12 weeks after the initial disability progression. Assessments occurring within 30 days after a protocol-defined relapse will not be used for confirmation of a disability progression. The non-confirmatory assessments (if any) should be at least equal to the minimum change required for progression.

For each component (EDSS and 9-HPT), missing assessments at scheduled visits prior to the last assessment of a patient, i.e. intermediate missing data, will not be replaced; progression detection or confirmation will be delayed to the next available assessment.

The hazard ratio will be estimated from a Cox regression, stratified by the randomization factors. The p-value will be calculated from a log-rank test, stratified by the randomization stratification factors.

In addition, a sensitivity analysis that adjusts for sex and *other prognostic factors* will be performed to assess the impact of these prognostic factors.

The handling of intercurrent events and missing data is described in Section 6.4.1.1.

6.4.1.1 Estimands for the Primary Analysis

The primary analysis has two co-primary estimands (see ICH E9 [R1] addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials; EMA 2017).

Co-primary estimand 1 follows a combination of treatment-policy and hypothetical strategies and estimates the treatment effect in the MRI-active subgroup of ocrelizumab versus placebo, regardless of adherence to the randomized treatment had the patients not initiated another MS DMT or commercial ocrelizumab on the basis of the following attributes:

a) *Population: Patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (See Sections 4.1.1 and 4.1.2 of the protocol), with magnetic resonance imaging (MRI) activity (See Section 2.1.1 of the protocol).*

b) *Treatment: Ocrelizumab IV 300mg administered at Day 1 and Day 14, followed by Ocrelizumab IV 600 mg administered every 24 weeks versus matching placebo.*

c) Variable: The variable will be time *to onset of composite 12-week CDP.*

d) Intercurrent events will be handled as follows:

- Withdrawal from treatment *and no initiation of another MS DMT or commercial ocrelizumab: Patients* will be followed regardless of adherence to study treatment or reason for withdrawal, and data will be collected and included in the analysis, following a treatment-policy strategy.
- *Withdrawal from treatment and* initiation of another MS DMT or commercial ocrelizumab: Future disease progression in the hypothetical scenario as if no other therapy had been initiated is predicted on the basis of previously observed data and the preceding reason for withdrawal from study treatment. The following strategies will be used:
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of initiation of another treatment.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as a disability progression event if the patient had an initial *disability progression* at *the date of* his or her last *EDSS or* 9-HPT

assessment prior to the initiation of another treatment, *whichever is the earliest*

Censored in all other cases at the date of the last *EDSS or 9-HPT assessment* prior to the initiation of another treatment,*whichever is the earliest*

- Withdrawal from study (missing data):
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of withdrawal from the study.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as a disability progression event if the patient had an initial *disability progression at the date of* his or her last *EDSS or* 9-HPT *assessment*, *whichever is the earliest*

    Censored in all other cases at the *date of the last EDSS or 9-HPT assessment, whichever is the earliest*

- The switch to PDP OCR has no impact on this efficacy endpoint because it can only occur after a confirmed disability progression in 9-HPT and EDSS (see Section 3.1.1.3). Patients who experience a DPE during the double-blind treatment phase will be given the option to switch to PDP OCR after they completed at least 120 weeks of double-blind treatment.

e) Population-level-summary estimator: The hazard ratio will be calculated from a Cox-regression to estimate the treatment-benefit, and the log-rank p-value will be used to test the statistical significance. Both will be stratified by the stratification factors from the randomization.

Patients without any disability progression events (including imputed events) during the double-blind treatment period will be censored at the date of the last EDSS or9-HPT assessment during the double-blind treatment period, whichever is the earliest.

Sensitivity analyses for co-primary estimand 1:

- A tipping-point analysis will be performed to assess the impact of the assumptions for patients who had an initial progression just before initiation of another MS DMT or commercial ocrelizumab, or withdrawal from study. In this analysis, the impact of different disability progression probabilities between 0 and 100% by randomized treatment arm will be assessed.
- Sensitivity analysis will be performed where the observed profile of patients in the placebo group is used to impute time to event for patients experiencing censoring because of the following:
  - Initiation of another MS DMT or commercial ocrelizumab
  - Withdrawal from study (missing data)

Supplementary estimand applying treatment-policy strategy to withdrawal from study treatment and to initiation of other treatments:

This supplementary estimand will use a treatment-policy strategy to estimate the treatment effect of ocrelizumab versus placebo on disability progression, on the basis of initial treatment, regardless whether patients adhered to randomized treatment or initiated other treatments (e.g., discontinued treatment or switched to another MS DMT or commercial ocrelizumab).

Supplementary estimand to estimate the treatment effect had the patient not withdrawn from study treatment:

The supplementary estimand will use a hypothetical strategy to estimate the treatment effect of ocrelizumab versus placebo on disability progression had the patient not withdrawn from study treatment as follows:

- The same estimand as the primary analysis for the Oratorio study (WA25046):

  If the patient withdraws from treatment *without any prior events*, an event is imputed as if the patient had an initial *disability progression* at *the date of* his or her last *EDSS or* 9-HPT *assessment* prior to withdrawal from treatment, *whichever is the earliest,* and no follow-up data are available, otherwise the patient is censored *in all other cases* at *the date of the last EDSS or 9-HPT assessment* prior to withdrawal from treatment, *whichever is the earliest*.

- Estimand counting withdrawal due to lack of efficacy as treatment failure:

  This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy (composite endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy will also have an imputed event.

- Estimand counting withdrawal due to lack of efficacy or due to adverse events as treatment failure:

  This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy or due to an adverse event (composite endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy or due to an adverse event will also have an imputed event.

Co-primary estimand 2 will be similar to the co-primary estimand 1 except the population will be *patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (See Sections 4.1.1 and 4.1.2 of the protocol).*

6.4.1.2 Estimands for the *Key* Secondary Endpoint of Time to Confirmed Disability Progression

6.4.1.2.1 *Estimands for the Key Secondary Endpoint of Time to 12-week Confirmed Disability Progression in 9-HPT*

The estimand for the *key* secondary endpoint of *time to* 12-week CDP *in 9-HPT* follows the same combination of treatment-policy and hypothetical strategies as for the primary endpoint but using the variable time to *12-week* CDP *in 9-HPT*. This will estimate the treatment effect of ocrelizumab versus placebo, regardless of adherence to the randomized treatment, had the patients not initiated another MS DMT or commercial ocrelizumab on the basis of the following attributes:

a) Population: *Patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (See Sections 4.1.1 and 4.1.2*).

b) *Treatment: Ocrelizumab IV 300mg administered at Day 1 and Day 14, followed by Ocrelizumab IV 600 mg administered every 24 weeks versus matching placebo.*

c) Variable: The variable will be time to 12-week CDP *in 9-HPT.*

d) Intercurrent events will be handled as below:

- Withdrawal from treatment *and no initiation of another MS DMT or commercial ocrelizumab*: Patients will be followed regardless of adherence to study treatment or reason for withdrawal, and data will be collected and included in the analysis, following a treatment-policy strategy.
- *Withdrawal from treatment and* initiation of another MS DMT or commercial ocrelizumab: Future disease progression in the hypothetical scenario as if no other therapy had been initiated is predicted on the basis of previously observed data and the preceding reason for withdrawal from study treatment. The following strategies will be used:
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of initiation of another treatment.
  - Withdrawal from study treatment due to another reason will be:

    Imputed as an event if the patient had an initial increase of *20% in 9-HPT time* at *the date of* his or her last *9-HPT* assessment prior to the initiation of another treatment

    Censored *in all other cases* at the *date of the* last *9-HPT* assessment prior to the initiation of another treatment
- Withdrawal from study (missing data):
  - If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of withdrawal from study.
  - Withdrawal from study treatment due to another reason will be:

Imputed as an event if the patient had an initial increase of *20% in 9-HPT time* at *the date* his or her last *9-HPT* assessment

Censored in all other cases at the date of the last 9-HPT assessment

e) Population-level-summary estimator: The hazard ratio will be calculated from a Cox-regression to estimate the treatment benefit, and log-rank p-value will be calculated to test the statistical significance. Both will be stratified by the stratification factors from the randomization.

Patients without any events (including imputed events) during the double-blind treatment period will be censored at the date of the last 9-HPT assessment during the double-blind treatment period.

6.4.1.2.2 *Estimands for the Key Secondary Endpoint of Time to 12-week Confirmed Disability Progression in EDSS*

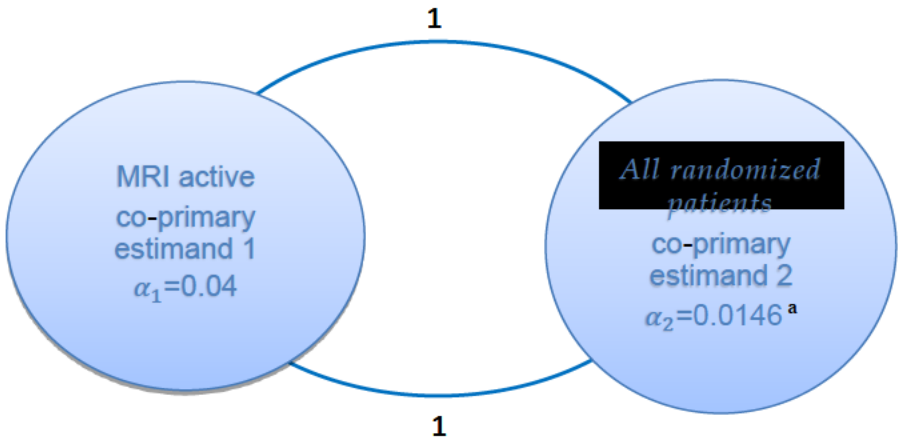
The estimand for the secondary endpoint of time to 12-week CDP in EDSS will be similar to the estimand for the secondary endpoint of time to 12-week CDP in 9-HPT with the variable being time to 12-week CDP in EDSS.

6.4.1.3 Control of the Type I Error

The primary analysis will be performed after the last randomized patient reaches the 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event) *or when at least 340 events are reached, whichever occurs earlier.*

The type 1 error will be controlled for the co-primary estimands with a fallback and loopback procedure, with an alpha of 0.04 for the MRI-active subgroup. The alpha for the all randomized population will be calculated according to Spiessens-Debois method (2010), the final proportion of information in the MRI-active subgroup. For example, if 36% (*122* of *340*) of all events in all randomized patients have occurred in the MRI-active subgroup, the alpha for the all randomized population will be 0.0146 (see Figure 3).

Figure 3 Graphical Representation of the Control of the Type I Error



MRI = magnetic resonance imaging.

[a] The a level indicated for estimand 2 is an example assuming that 36% (122 of 340) of all events in all randomized patients have occurred in the MRI-active subgroup. The actual alpha level for the primary analysis will be determined based on the actually observed events based on the Spiessens-Debois method.

Calculation of α_1 and α_2 will be as follows:

α_1 is arbitrarily chosen as 0.04, to maximize the power of the analysis for the MRI-active subgroup.

α_2: calculated according to the Spiessens-Debois method (2010). For example of α_2 calculated assuming 122 events in MRI-active subgroup and 340 events in the ITT, $\alpha_2 = 0.0146$. a_2 will be calculated at the primary analysis, with the proportion of information in the MRI-active subgroup.

Fallback: If the analysis of the co-primary estimand 1 has a p-value < 0.04, then the analysis for the co-primary estimand 2 will be tested with $\alpha = 0.05$.

Loop-back: If the analysis of the co-primary estimand 2 has a p-value < 0.0146, then the co-primary estimand 1 will be tested with $\alpha = 0.05$.

If at least one of the two co-primary estimands is statistically significant, then the trial is positive.

If only one of the co-primary estimands is positive, the secondary endpoints will be tested for all randomized patients and the MRI-active subgroup but the p-value will not be formally controlled.

If both co-primary estimands are statistically significant, then the secondary endpoints will be tested with $\alpha = 0.05$.

The secondary endpoints will be tested in a hierarchical gatekeeping procedure for all randomized patients, and as exploratory in the MRI-active subgroup.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo for all randomized patients on the basis of the following endpoints, in hierarchical order:

- *Time to 12-week CDP in 9-HPT*
- Time to 12-week CDP in EDSS
- *Time to 24-week CDP in 9-HPT*
- Time to 24-week CDP in EDSS
- Differences in the *annual rate of* percent change *from baseline* in total volume of T2 lesions on MRI *scans* will be analyzed using *a random coefficient regression model (RCRM)*

- Differences in the *annual rate of percent* change *from Week 24* in total brain volume on MRI scans will be analyzed using an *RCRM* analysis

The estimand for the secondary endpoint of *time to 12-week CDP in 9-HPT* and *time to* 12-week CDP in EDSS is described in *Sections 6.4.1.2.1 and 6.4.1.2.2, respectively*.

6.4.3 Exploratory Efficacy Endpoints

The secondary efficacy endpoints will also be evaluated as exploratory analyses for the MRI-active subgroup.

An exploratory efficacy objective for this study is to evaluate the efficacy of ocrelizumab compared with placebo on the primary and secondary endpoints in the subgroup of patients ages >55 versus ≤ 55, patients with EDSS score ≤ 6.5 versus >6.5, males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup), and in the MRI-inactive subgroup versus MRI-active subgroup. Because the above subgroups of patients ages >55 and with EDSS score >6.5 were not enrolled in the previous PPMS study (WA25046), there is a special interest in analyzing these subgroups. An MRI-active subgroup is a co-primary endpoint; therefore, the complementary MRI-inactive subgroup will also be analyzed.

Other exploratory analyses for all randomized patients and MRI-active subgroup are on the basis of the following endpoints:

- Change from baseline to Week 120 in fatigue as measured by MFIS
- *Annual rate of percent* change from baseline and from Week 24 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in ABILHAND
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Neuro-QoL-UE)
- Change from baseline to Week 120 in the PGIC-UL function
- Change from baseline to Week 120 in the PGIC-F
- Change from baseline to Week 120 in the MSIS-29 physical score
- Proportion of patients at Week 120 with a pre-specified, clinically meaningful decline on the MSIS-29
- Change from baseline to Week 120 in the SDMT
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight RPM)
- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI
- *Annual rate of percent* change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one infusion (partial or complete) of study drug (ocrelizumab or placebo), with patients grouped according to treatment received.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

The main safety objective for this study is to evaluate the safety of ocrelizumab compared with placebo until when patients receive any PDP OCR, commercial ocrelizumab treatment, or other MS DMT in all patients who receive at least one infusion (partial or complete) of study drug (ocrelizumab or placebo).

The safety endpoints considered are as follows:

- Adverse events leading to study treatment withdrawal
- Adverse events in patients previously treated with an another DMT for MS
- Proportion of patients with adverse events and serious adverse events
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- Vital signs (blood pressure and pulse rate) during and 1 hour after infusion
- Change from baseline in laboratory test results for hematology and chemistry
- Change from baseline in laboratory test results for immunoglobulins (IgA, IgM, IgG) and T-cell subtype (CD3, CD4, CD8): MMRM analyses will be performed. Fixed effects in the model will include treatment arm, visit, treatment by visit interaction, stratification factors, baseline value of the immunoglobulin or T-cell, and baseline by visit interaction. Visits will be treated as a repeated variable within a patient. Patient, treatment, and visit will be treated as factor variables. An unstructured variance-covariance structure will be applied to model the within-patient errors. Appropriate variance stabilizing transformations of the laboratory measurements (e.g., log-transformation) may be applied.
- Association of decrease in each immunoglobulin (IgA, IgM, IgG) and serious infections: incidence rate of serious infections per 100 PY during the episodes of confirmed drop of immunoglobulin levels below LLN versus the incidence rate of serious infections per 100 PY in the remaining exposure (before or after a confirmed drop, and during the overall exposure for the patients without any confirmed drop of immunoglobulin) for each treatment arm. The exposure of a confirmed episode is counted from the day the immunoglobulin first decreased below LLN until the day it is normalized above LLN, and the serious infections with onset date in between are counted. The 95% confidence interval will be calculated using Poisson distribution methods.
- Association of decrease in each T-cell subtype (CD3, CD4, CD8) and serious infections will be analyzed as for the immunoglobulin described above.

Additional safety objectives for this study will include evaluation of the following:

- Subgroup analyses: patients with MRI-active versus MRI-inactive, patients aged ≤ 55 versus > 55 years, patients with a baseline EDSS score of ≤ 6.5 versus > 6.5, females and males, and patients previously treated (prior to randomization) with another DMT for MS
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- Pharmacodynamics, as measured by B-cell levels in blood

The ocrelizumab pool for long-term safety analysis will consist of all randomized patients who received at least one infusion (partial or complete) of ocrelizumab (study drug, PDP OCR, or commercial ocrelizumab) until when patients receive any other MS DMT as follows:

- Adverse events leading to withdrawal of ocrelizumab treatment
- Adverse events in patients previously treated with another DMT for MS
- Proportion of patients with adverse events and serious adverse events
- Incidence rates per 100 PY for infections, serious infections, death, and malignancies, including breast cancer
- Change from first administration of ocrelizumab in laboratory test results for hematology and chemistry
- Change from first dose of ocrelizumab in immunoglobulins (IgA, IgM, IgG) and T-cell subtype (CD3, CD4, CD8)
- Associations of decrease in each immunoglobulin (IgA, IgM, IgG) and serious infections
- Associations of decrease in each T-cell subtype (CD3, CD4, CD8) and serious infections

In an exploratory analysis, all safety analyses will be conducted on data collected from the first ocrelizumab dose until the end of the study.

6.6 PHARMACOKINETIC ANALYSES

PK analysis of ocrelizumab serum concentration versus time data will be conducted using a population PK approach. Nonlinear mixed effects modeling (with software NONMEM) will be used to analyze the sparse sampling dose-concentration-time data of ocrelizumab. Patients who have measurable concentrations of ocrelizumab will be included in the PK analysis unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred that would interfere with PK evaluation. The PK data of this study may be pooled with data from other studies. Population PK parameters (e.g., clearances and volumes) will be estimated and the influence of covariates, such as sex, body weight, and baseline CD19 lymphocytes, on these parameters will be investigated. Exposure (area under the concentration-time

curve) to ocrelizumab will be estimated. The selection of other parameters will depend on the final PK model used for this analysis. Additional PK analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Pharmacodynamic biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time and/or proportion of participants with biomarker levels within a defined threshold over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Descriptive or summary statistics will be used to describe biomarker assessments.

NfL treatment response will be presented as absolute values over time, percent change relative to baseline over time, and/or proportion of participants with NfL levels below a pre-defined threshold over time.

Baseline NfL levels or NfL levels on treatment determined by the appropriate assay and to be determined pre-defined cutoffs will be used to assess the relationship of baseline or on-treatment NfL to future efficacy, imaging, or other outcomes.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

There is no planned interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent

Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior

to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

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

At least 220 sites globally are estimated to participate to enroll approximately 1000 patients, of which at least 350 patients are planned to be in the MRI-active subgroup. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed. Monitoring details will be described in the iDMC Charter.

An external Steering Committee will provide general guidance, assist with liaison to investigators and oversee any external communication of the results of the study. The external Steering Committee will stay blinded to all data until the primary analysis.

9.6 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, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation,

and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities: Double-Blind Treatment

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
Informed consent[e]	x														
Review of eligibility criteria	x	x													
Demographic data	x														
Medical history and baseline conditions	x														
PROs (ABILHAND, Neuro-QoL-UE, MFIS, MSIS-29)[f]	x	x			x		x		x		x				x
PGIC-F, PGIC-UL[f]					x		x		x		x				x
EQ-5D-5L[f]		x			x		x		x		x				x
Vital signs[g]	x	x	x	x	x		x		x		x		x		
Weight, height		x													
Physical examination[h]	x	x			x		x		x		x		x		x
Neurological examination[i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
9-HPT[j]	x	x		x	x	x	x	x	x	x	x	x		x	x
EDSS[k]	x	x		x	x	x	x	x	x	x	x	x		x	x
SDMT		x			x		x		x		x				x
Hematology, chemistry, urinalysis[l]	x	x		x	x	x	x	x	x	x	x	x			x
Flow cytometry (including CD3/4/8/19 count)[m]	x	x	x		x		x		x		x		x		x

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
CD4				x		x		x		x		x			
IgG, IgA, IgM	x	x		x		x		x		x		x			x
CSF sample (if required; Week 48 optional)[n]	x						x[n]								
Pregnancy test (if applicable)[o]	x	x	x		x		x		x		x		x		
FSH level (if applicable)[p]	x														
Review of re-treatment criteria			x		x		x		x		x		x		
Pretreatment with IV methylprednisolone and antihistaminic[q]		x	x		x		x		x		x		x		
Administration (infusion) of ocrelizumab/placebo[r]		x	x		x		x		x		x		x		
Concomitant medications[s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events[t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mandatory MRI[u]	x				x		x		x		(x)				x
Optional additional cervical spinal cord MRI[u]	x				x										x
ADA sample (serum)[v]		x			x		x		x		x				x
PK sample (serum)[w]		x	x	x	x		x	x	x		x				x
Biomarker plasma and serum samples[x]		x	x	x	x		x		x		x				x
DNA genotyping sample[y]		x													

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

	Screen.	Double-Blind Treatment											Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose		1			2		3		4		N[d]				
Visit	1	2	3	4	5	6	7	8	9	10	n	N			
Study week		0	2	12	24	36	48	60	72	84	n	n + 12 wks			
(Window in days)	–168 to –1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7			
RBR RNA and RBR plasma samples (optional)[z]		x	x	x	x		x		x		x	x			
RBR DNA sample (optional)[z]		x													
Digital outcome assessments (Floodlight RPM) (optional)[aa]	x	x	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –
Hepatitis B screening[bb]	x														
Hepatitis B virus DNA[bb] (if required)				x	x	x	x	x	x	x	x	x			x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; CSF = cerebrospinal fluid; Discon. = discontinuation; EC = Ethics Committee; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; IRB = Institutional Review Board; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; PDP OCR = post-double-progression ocrelizumab; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; RBR = Research Biosample Repository; RPM = remote patient monitoring; Screen. = screening; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; WGS = whole genome sequencing; (x) = every 48 weeks.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding the double-blind treatment phase, see Section 3.1.1.2. See Figure 2 for information regarding how a patient proceeds through the different study phases.

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

[b] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[c] Patients who discontinue study drug prematurely from the double-blind treatment phase will return to the clinic for a treatment discontinuation visit.

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

[d] The assessments required for N represent the typical schedule of assessments for the double-blind treatment phase with Week 144 being the last visit. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.

[e] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment and PDP OCR (if applicable).

[f] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L. Questionnaires will be completed every 6 months during the double-blind treatment phase. EQ-5D-5L will not be completed at screening. PGIC-UL and PGIC-F will not be completed at screening and baseline.

[g] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab (or placebo) infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] At screening, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[j] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[k] EDSS including functional system scores will be assessed and collected.

Appendix 1: Schedule of Activities: Double-Blind Treatment (cont.)

[l] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).

[m] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[n] CSF sample will only be required at screening for patients who do not have documented history of elevated IgG index and/or one or more IgG oligoclonal bands detected by isoelectric focusing. The CSF specimen will be sent out to the central laboratory to verify presence of elevated IgG index and IgG oligoclonal bands. Leftover CSF will be stored by the central laboratory for biomarker use. Patients for whom screening CSF was collected will have the option to participate in a collection of CSF at Week 48. The CSF sample should be collected prior to the ocrelizumab (or placebo) infusion at Week 48 (within a window of 14 days prior to the actual scheduled visit Week 48). This sample will be used for exploratory biomarker determination.

[o] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

[p] Testing of the FSH level is only applicable to female patients to confirm the post-menopausal status at screening. The sample will be analyzed by the central laboratory.

[q] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV *(or equivalent oral dose of prednisolone or methylprednisolone should IV methylprednisolone not available)* and an oral or IV antihistamine (e.g., IV 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 (or placebo) 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 patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab (or placebo) infusion.

[r] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[s] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

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

[u] At screening, two mandatory MRI scans will be performed at least 6 weeks apart or one mandatory MRI that can be compared with a historical MRI performed in the previous 1 year to be used for eligibility determination. The mandatory MRI performed closer to randomization will be considered the baseline MRI for the study analyses and should be obtained from 6 weeks up to 10 days prior to randomization. During the study conduct, mandatory MRI scans should occur within ± 4 weeks of the scheduled visit. In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at treatment discontinuation visit) if one was not performed during the prior 4 weeks. From Week 72 onward, mandatory MRI scans will be performed every 48 weeks. The mandatory MRI sequences are comprised of both brain and upper cervical spinal sequences if site technology is available. Cervical spinal sequences are not required for the first mandatory MRI at screening MRI nor are expected to be included in a historical MRI used for screening (if applicable), but these sequences should be included in second mandatory MRI scan (considered the baseline MRI). Additional optional, cervical spinal cord MRI sequences may be acquired for baseline, Weeks 24 and 120, and at treatment discontinuation. Additional optional MRI sequences are not required to accompany the first mandatory MRI at screening MRI, nor are expected to be included in a historical MRI used at screening (if applicable), but these sequences should be included in the second mandatory MRI (considered the baseline MRI) scan. At the Week 120 visit for patients switching to PDP OCR treatment, mandatory MRI scans should be obtained within 4 weeks before the Week 120 visit.

[v] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[w] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. At study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[x] Plasma and serum samples will be collected before the initial study drug dose at Visit 2 as well as Visits 3, 4, and 5; and every 6 months following for biomarkers during double-blind treatment, as indicated.

[y] A single mandatory DNA sample will be collected for patient genotyping at the baseline visit. If the DNA sample is not collected at the baseline visit, it may be collected at any subsequent visit. Collection and submission of this sample is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling (see Section 4.5.13), collection of this sample will not be applicable at that site.

[z] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA and a RBR plasma sample collected at all indicated visits.

[aa] Digital outcome assessments are optional only. Patients who choose to and consent to the optional digital outcome assessments at screening will be asked to begin performing digital assessments 4 weeks prior to baseline (i.e., Days –28 to 1; see Section 4.5.15).

[bb] All patients must have negative HBsAg test result at screening prior to enrollment. If total HBcAb is positive at screening, HB virus DNA measured by PCR must be negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 12 weeks during double-blind treatment phase.

Appendix 2
Schedule of Activities: Follow-Up 1 (and PDP OCR)

	FU1 [a]						Delayed Dosing Visit [b]	Unschd. Visit [c]	Tx Discon. Visit [d]	EOO or WD from FU
	Follow-up	PDP OCR								
Dose	Visits every 12 wk (± 7 d)	1			N [e]					
Visit		1	2	3	n	n				
Study week		0	2	12	n	n+ 12wk				
(Window in days)			±2	±7	±5	±7				
Informed consent [f]		x								
PROs (ABILHAND, Neuro-QoL-UE, MFIS, MSIS-29) (every 48 weeks) [g]	(x)	x			(x)				x	
PGIC-F, PGIC-UL (every 48 weeks) [g]	(x)	x			(x)				x	
EQ-5D-5L (every 48 weeks) [g]		x			(x)				x	
Vital signs [h]		x	x	x	x		x			
Physical examination [i]	x	x			x		x		x	x
Neurological examination [j]	x	x	x	x	x	x	x	x	x	x
9-HPT [k]	x	x		x	x	x		x	x	x
EDSS [l]	x	x		x	x	x		x	x	x
SDMT	x	x			x			x	x	x
Hematology, chemistry, urinalysis [m]	x	x		x	x	x			x	x
Flow cytometry (including CD3/4/8/19 count) [n]	x	x	x		x		x		x	x
CD4				x		x				
IgG, IgA, IgM	x	x		x		x			x	
Pregnancy test (if applicable) [o]		x	x		x		x			
Review of re-treatment criteria		x	x		x		x			
Pretreatment with IV methylprednisolone and antihistaminic [p]		x	x		x		x			
Administration (infusion) of ocrelizumab [q]		x	x		x		x			

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

	FU1[a]						Delayed Dosing Visit[b]	Unschd. Visit[c]	Tx Discon. Visit[d]	EOO or WD from FU
	Follow-up	PDP OCR								
Dose	Visits every 12 wk (± 7 d)	1			N[e]					
Visit		1	2	3	n	n				
Study week		0	2	12	n	n+ 12wk				
(Window in days)			±2	±7	±5	±7				
Concomitant medications[r]	x	x	x	x	x	x	x	x	x	x
Adverse events[s]	x	x	x	x	x	x	x	x	x	x
Mandatory MRI (every 48 weeks)[t]	(x)	(x)			(x)				x	x
ADA sample (serum)[u]	x	x			x				x	
PK sample (serum)[v]	x	x	x	x	x				x	
Biomarker plasma and serum samples[w]		x	x	x	x					x
RBR RNA and RBR plasma samples (optional)[x]		x	x	x	x					x
Digital outcome assessments (Floodlight RPM) (optional)[y]	x	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - →
Hepatitis B virus DNA[z] (if required)	x	x		x	x	x			x	x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; Discon. = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; EOO = end of observation; FU = follow up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; WD = withdrawal; Wk = week; (x) = every 48 weeks.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding eligibility for and duration of PDP OCR and FU1, see Sections 3.1.1.3 and 3.1.1.4, respectively. See Figure 2 for information regarding how a patient proceeds through the different study phases (including FU1 and PDP OCR).

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

[a] The FU1 phase will run in parallel with the double-blind treatment phase until 144 weeks from randomization for each patient *or until the primary analysis*. Scheduled visits will be performed every 12 weeks and will include both efficacy and safety assessments. For patients receiving PDP OCR, patients must sign the optional PDP OCR informed consent form. Patients who experience a double-progression event during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment. PDP OCR treatment phase will continue until the end of the OLE phase. Assessments in FU1 and PDP OCR phases that only need to be performed annually are marked in brackets (x).

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

[c] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[d] Patients who discontinue study drug prematurely from the PDP OCR treatment phase will return to the clinic for a treatment discontinuation visit.

[e] The PDP OCR can be terminated at any time up to the date at which the last data point is collected for the primary analysis (see Section 3.1.1.3). The assessments required for N represent the typical schedule of assessments for the PDP OCR phase. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.

[f] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment and PDP OCR (if applicable).

[g] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L. During FU1 and PDP OCR they will be completed every 48 weeks, starting Week 0 of FU1. EQ-5D-5L will only be completed during PDP OCR.

[h] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF page. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

[j] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[k] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[l] EDSS including functional system scores will be assessed and collected.

[m] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).

[n] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[o] Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

[p] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV *(or equivalent oral dose of prednisolone or methylprednisolone should IV methylprednisolone not available)* and an oral or IV antihistamine (e.g., IV 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 patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab (or placebo) infusion.

[q] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[r] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

Appendix 2: Schedule of Activities: Follow-Up 1 (and PDP OCR) (cont.)

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

[t] During the study conduct, mandatory MRI scans should occur within ± 4 weeks of the scheduled visit and will be performed every 48 weeks. In addition, mandatory MRI scans will be obtained in patients who withdraw from study treatment (at Tx Discon, WD from FU or EOO visit) if one was not performed during the prior 4 weeks.

[u] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[v] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. At study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[w] Plasma and serum samples will be collected as indicated. Only to be collected for WD from FU visits performed before start of OLE.

[x] These sample types to be collected for research purposes if patient agrees to separate optional RBR consent—a single RBR DNA sample at baseline visit (or any subsequent visit if missed), and an RBR RNA and a RBR plasma sample collected at all indicated visits. Only to be collected for WD from FU visits performed before start of OLE.

[y] Digital outcome assessments are optional only.

[z] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 12 weeks during FU1 and PDP OCR.

Appendix 3
Schedule of Activities: Open-Label Extension

	OLE Screening	OLE [d]									Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose		1			2		3		N [d]				
Visit		1	(2)	3	4	5	6	7	n	n			
Study week		Wk 0	Wk 2	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	n	n + 22 wk			
(Window in days)	–30 to –1		(±2)	(±7)	(±5)	(±7)	(±5)	(± 7)	(±5)	(±7)			
Informed consent [e]	x												
Review of eligibility criteria	x												
PROs (ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, EQ-5D-5L) [f]		x					x		x				x
Vital signs [g]		x	x		x		x		x		x		
Physical examination [h]		x			x		x		x		x		x
Neurological examination [i]		x	x	x	x	x	x	x	x	x	x	x	x
9-HPT [j]		x			x		x		x			x	x
EDSS [k]		x			x		x		x			x	x
SDMT		x			x		x		x				x
Hematology, chemistry, urinalysis [l]	x	x		x		x		x		x			x
Flow cytometry (including CD3/4/8/19 count) [m]		x		x		x		x		x	x		x
CD4	x			x		x		x		x			
IgG, IgA, IgM	x			x		x		x		x			x
Pregnancy test (if applicable) [n]	x	x	x		x		x		x		x		
Review of re-treatment criteria		x	x		x		x		x		x		
Pretreatment with IV methylprednisolone and antihistaminic [o]		x	x		x		x		x		x		

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

	OLE Screening	OLE [d]									Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose		1			2		3		N [d]				
Visit		1	(2)	3	4	5	6	7	n	n			
Study week		Wk 0	Wk 2	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	n	n + 22 wk			
(Window in days)	–30 to –1		(±2)	(±7)	(±5)	(±7)	(±5)	(± 7)	(±5)	(±7)			
Administration (infusion) of ocrelizumab [p]		x	x		x		x		x		x		
Concomitant medications [q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [r]	x	x	x	x	x	x	x	x	x	x	x	x	x
Mandatory MRI (every 48 weeks) [s]		(x)			(x)		(x)		(x)				x
Additional optional cervical spinal cord MRI (every 48 weeks) [s]		(x)			(x)		(x)		(x)				x
ADA sample (serum) [t]		x					x		x				x
PK sample (serum) [u]		x					x		x				x
Hepatitis B virus DNA (if required) [v]	x	x		x		x		x		x			x

9-HPT = 9-Hole Peg Test; ADA = anti-drug antibody; Discon. = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MFIS = Modified Fatigue Impact Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale-29; Neuro-QoL-UE = Quality of Life in Neurological Disorders-Upper Extremity Function; OLE = open-label extension; PGIC-F = Patient Global Impression of Change for Fatigue; PGIC-UL = Patient Global Impression of Change for Upper Limb Function; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; PRO = patient-reported outcome; SDMT = Symbol Digit Modalities Test; Tx = treatment; Unschd. = unscheduled; Wk = week; (x) = every 48 weeks.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. On infusion days, all assessments should be performed prior to dosing, unless otherwise specified. For more information regarding eligibility for and duration of the OLE, see Section 3.1.1.5. See Figure 2 for information regarding how a patient proceeds through the different study phases (including OLE).

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

[b] Assessments at unscheduled (non-dosing) visits may be performed as clinically appropriate.

[c] Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit.

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

[d] *Each* patient will remain in the OLE phase for at least 2 years (at least 4 doses of ocrelizumab). The assessments required for N represent the typical schedule of assessments for the OLE phase. If the study ends for any reason or the patient must be withdrawn from treatment, a treatment discontinuation visit should be performed.

[e] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[f] Questionnaires will be self-administered prior to the administration of study treatment. The questionnaires should be completed before the patient receives any information on disease status, prior to the administration of non-PRO assessments, and in the following order each time, whenever possible: ABILHAND, Neuro-QoL-UE, PGIC-UL, MFIS, PGIC-F, MSIS-29, and EQ-5D-5L.

[g] Includes pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Temperature should be measured and recorded in patient's notes only. Blood pressure and pulse rate will be recorded on the appropriate eCRF. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone infusion. In addition, blood pressure and pulse rate should be obtained prior to start of infusion, every hour during the infusion, at the end of infusion and 1 hour after the end of the infusion. On non-infusion days, the vital signs may be taken at any time during the visit. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[j] Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand) (National Multiple Sclerosis Society 2001).

[k] EDSS including functional system scores will be assessed and collected.

[l] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).

[m] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[n] Urine pregnancy tests will be performed at specified visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β-hCG (sensitivity of at least 25 mU/mL) will be performed locally.

Appendix 3: Schedule of Activities: Open-Label Extension (cont.)

[o] Patients will receive prophylactic treatment with 100 mg of methylprednisolone IV *(or equivalent oral dose of prednisolone or methylprednisolone should IV methylprednisolone not available)* and an oral or IV antihistamine (e.g., IV 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 patient, use of an equivalent dose of an alternative steroid should be used as premedication prior to the infusion. It is also recommended that patients receive an analgesic/antipyretic such as acetaminophen/paracetamol (1 g) 30–60 minutes prior to ocrelizumab infusion.

[p] The investigator must review the clinical and laboratory re-treatment criteria prior to subsequent infusion of ocrelizumab. The patient will need to remain under observation at the clinical site for at least 1 hour after infusion. At infusion visits, it is anticipated that the patient will need to stay at the hospital or clinical site for a full day.

[q] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

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

[s] MRI scans should occur within a window of ±4 weeks of the scheduled visit. In addition, mandatory MRI scans and additional optional cervical spinal MRI scans (if applicable) will be obtained in patients who withdraw from study treatment (at treatment discontinuation visit) if one was not performed during the prior 4 weeks. During the OLE, mandatory MRI scans *and additional optional sagittal cervical spinal cord scans* will be performed every 48 weeks indicated by (x) (according to the yearly schedule as carried over from the double-blind treatment phase).

[t] Serum sample, to be taken prior to the IV methylprednisolone infusion.

[u] On study drug infusion days, two serum samples (one prior to the IV methylprednisolone infusion, and one within 30 minutes after completion of study drug infusion) will be collected. On visits without study drug infusion, PK sample may be collected at any time. During study drug infusion visits, PK samples will be collected from the arm opposite to the infusion.

[v] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

Appendix 4
Schedule of Activities: Follow-Up 2

	FU2 [a]	EOO or WD from FU
Study week	*Week 24 (24 wks after the last visit in DBT, OLE, PDP OCR or FU1 phases)*	
(Window in days)	(±7 d)	
Physical examination [c]	x	x
Neurological examination [d]	x	x
Hematology, chemistry, urinalysis [e]	x	x
Flow cytometry (including CD3/4/8/19 count) [f]	x	x
IgG, IgA, IgM	x	
Concomitant medications [g]	x	x
Adverse events [h]	x	x
MRI [i]		x
ADA sample (serum) [j]	x	
PK sample (serum) [k]	x	
Hepatitis B virus DNA (if required) [l]	x	x

ADA = anti-drug antibody; *DBT = double-blind treatment;* eCRF = electronic Case Report Form; EOO = end of observation; FU = follow up; *FU1 = follow-up 1;* HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; MRI = magnetic resonance imaging; MS = multiple sclerosis; *OLE = open-label extension; PDP OCR = post-double-progression ocrelizumab;* PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; WD = withdrawal; Wk = week.

Notes: All assessments should be performed on the day of the scheduled visit, unless otherwise specified. For more information regarding FU2, see Section 3.1.1.6. See Figure 2 for information regarding how a patient proceeds through the different study phases (including FU2).

[a] Laboratory and safety assessments performed during clinical visit *at* 24 weeks. All patients will continue in the FU2 *for 24 weeks after the last visit either in DBT, OLE, PDP OCR or FU1 phases wherever patient was at that time*. For information regarding FU2 duration and eligibility, refer to Section 3.1.1.6.

[b] At the end of FU2 phase *the patient will complete the study*.

[c] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 4: Schedule of Activities: Follow-Up 2 (cont.)

[d] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. All patients with new neurological symptoms suggestive of MS worsening should have EDSS assessment performed by Examining Investigator. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study treatment permanently.

[e] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), and quantitative platelet count. Chemistry includes AST, ALT, gamma-glutamyl transferase, total bilirubin, creatinine, amylase, potassium, and sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and clinically significant will be performed at the site (local laboratory).

[f] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry.

[g] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

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

[i] Mandatory MRI scans will be obtained in patients who withdraw from study (at WD from FU or EOO visit) if one was not performed during the prior 4 weeks.

[j] Serum samples may be collected at any time.

[k] PK sample may be collected at any time during the visit.

[l] For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (PCR) must be repeated every 24 weeks.

Appendix 5
Progressive Multifocal Leukoencephalopathy: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

ACTION STEPS IF PML IS SUSPECTED

- If the clinical presentation is suggestive of progressive multifocal leukoencephalopathy (PML) (see Table 1), further investigations should include brain magnetic resonance imaging (MRI) evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (Berger et al. 2013; Figure 1) a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) should be undertaken for the detection of JC virus (JCV) DNA by polymerase chain reaction using a validated sensitive assay. For details, refer to the most up to date laboratory manual providing storage conditions and shipment instructions. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF. This sample will be stored for 1 year after the last patient, last visit.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007).

MRI ASSESSMENT

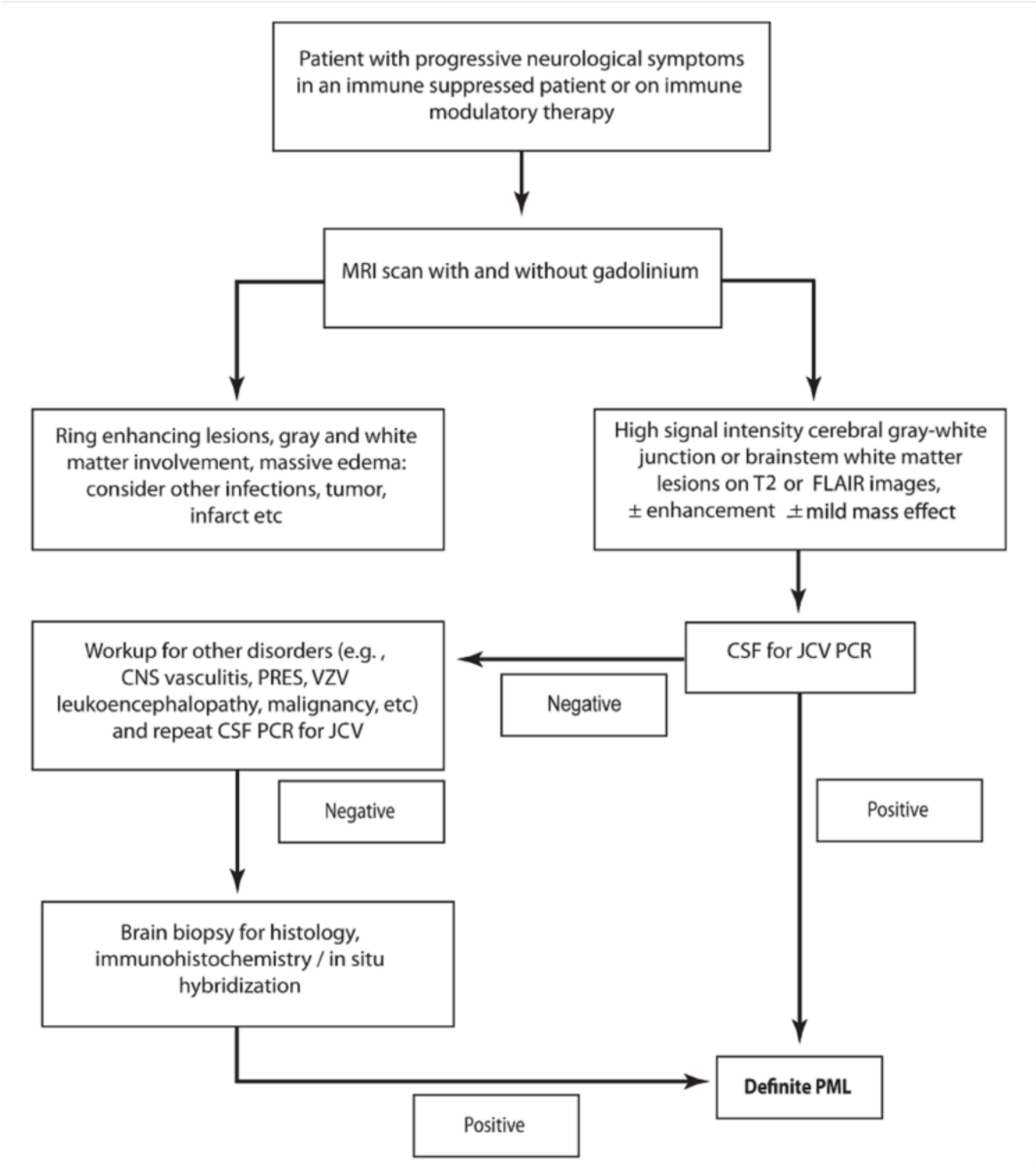
- Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a mandatory MRI scan that includes fluid-attenuated inversion recovery and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes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

CSF ASSESSMENT

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

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

Figure 1 Diagnostic Algorithm Framework for PML (Berger et al. 2013)



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

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

Table 1 Clinical Signs and Symptoms Typical of MS and PML

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

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Adapted from Kappos et al. 2007.

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

Table 2 MRI Lesion Characteristics Typical of PML and MS

Feature	Multiple Sclerosis	PML
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-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 T_1-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 T_2-weighted images
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.
Adapted from Yousry et al. 2006.

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

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Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. Lancet Neurol 2007;6:431–41.

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Appendix 6
EQ-5D-5L

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Health Questionnaire

English version for the USA

Appendix 6: EQ-5D-5L (cont.)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

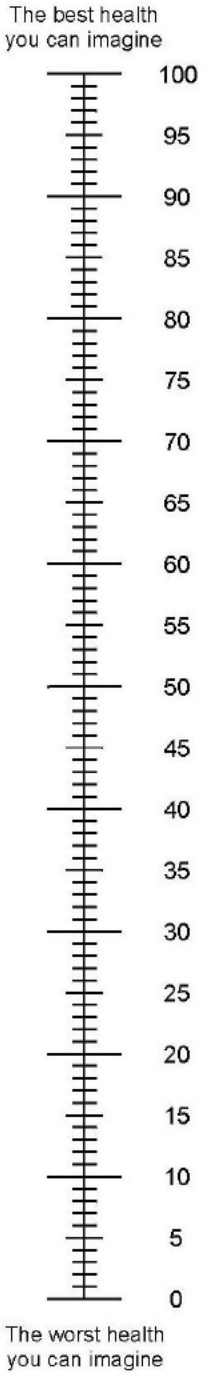
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7
Multiple Sclerosis Impact Scale, Version 2

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

- The following questions ask for your views about the impact of MS on your day-to-day life in the **past 14 days**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past 14 days, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past 14 days, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving around indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Feelings of heaviness in your arms and/or legs?	1	2	3	4
9. Tremors in your arms and/or legs?	1	2	3	4
10. Spasms in your arms and/or legs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

MSIS-29 - United States/English - Version of 22 Feb 13 - MAPI Institute.
ID7215 / MSIS-29_AU2.0_eng-US.doc

Multiple Sclerosis Impact Scale Version 2 (MSIS-29v2) continued				
In the past 14 days, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down on the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the bathroom urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

MSIS-29v2 2005

MSIS-29 - United States/English - Version of 22 Feb 13 - MAPI Institute.

ID7215 / MSIS-29_AU2.0_eng-US.doc

Appendix 8
Modified Fatigue Impact Scale

Patient's Name: _____ **Date:** _____/_____/_____
month day year

ID#: _____ **Test#:** 1 2 3 4

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 circle 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
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4

Appendix 8: Modified Fatigue Impact Scale (cont.)

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
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
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

Appendix 8: Modified Fatigue Impact Scale (cont.)

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
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**

Appendix 9
ABILHAND

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ABILHAND – English Version

	How DIFFICULT are the following activities?	Impossible	Very Difficult	Difficult	Easy	N/A
1.	Turning over the pages of a book					
2.	Pulling up the zipper of trousers					
3.	Peeling onions					
4.	Sharpening a pencil					
5.	Using a spoon					
6.	Using a screwdriver					
7.	Picking-up a can					
8.	Taking the cap off a bottle					
9.	Filing one's nails					
10.	Grasping a coin on a table					
11.	Closing a door					
12.	Washing one's face					
13.	Peeling potatoes with a knife					
14.	Turning off a tap					
15.	Buttoning up trousers					
16.	Dialling on a keypad phone					
17.	Opening a screw-topped jar					
18.	Cutting one's nails					
19.	Turning on a radio					
20.	Tearing open a pack of chips					
21.	Turning on a lamp					
22.	Combing one's hair					
23.	Unwrapping a chocolate bar					
24.	Hammering a nail					
25.	Replacing a light bulb					
26.	Inserting a diskette into a drive					
27.	Making pancake batter					
28.	Spreading butter on a slice of bread					
29.	Counting bank notes					
30.	Washing one's hands					
31.	Handling a stapler					

Please turn over

Appendix 9: ABILHAND (cont.)

	How DIFFICULT are the following activities?	Impossible	Very Difficult	Difficult	Easy	N/A
32.	Winding up a wrist watch					
33.	Turning a key in a keyhole					
34.	Turning on a television set					
35.	Brushing one's hair					
36.	Drawing					
37.	Ringing a door bell					
38.	Placing a glass of water on a table					
39.	Drinking a glass of water					
40.	Buttoning up a shirt					
41.	Threading a needle					
42.	Cutting meat					
43.	Eating a sandwich					
44.	Handling a 4 colour ballpoint pen with one hand					
45.	Blowing one's nose					
46.	Wrapping up gifts					
47.	Fastening the zipper of a jacket					
48.	Fastening a snap (jacket, bag, ...)					
49.	Writing a sentence					
50.	Shelling hazelnuts					
51.	Screwing a nut on					
52.	Opening mail					
53.	Typewriting					
54.	Squeezing toothpaste on a toothbrush					
55.	Taking a coin out of the pocket					
56.	Brushing one's teeth					

Appendix 10
Quality of Life in Neurological Disorders-Upper Extremity Function (Fine Motor, ADL)

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Upper Extremity Function (Fine Motor, ADL)

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA40	Are you able to turn a key in a lock?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA50	Are you able to brush your teeth?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX44	Are you able to make a phone call using a touch tone key-pad?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB21	Are you able to pick up coins from a table top?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA43	Are you able to write with a pen or pencil?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA35	Are you able to open and close a zipper?...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA22	Are you able to open previously opened jars?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB22	Are you able to hold a plate full of food?..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA47	Are you able to pull on trousers?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA54	Are you able to button your shirt?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB41	Are you able to trim your fingernails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX39	Are you able to cut your toe nails?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PAF9	Are you able to bend down and pick up clothing from the floor?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
June 18, 2018

Neuro-QoL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)

		No difficulty	A little difficulty	Some difficulty	A lot of difficulty	Can't do
NQUEX03	How much DIFFICULTY do you currently have using a spoon to eat a meal?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX04	How much DIFFICULTY do you currently have putting on a pullover shirt?.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX05	How much DIFFICULTY do you currently have taking off a pullover shirt?.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX06	How much DIFFICULTY do you currently have removing wrappings from small objects?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQUEX15	How much DIFFICULTY do you currently have opening medications or vitamin containers (e.g., childproof containers, small bottles)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
June 18, 2018

Appendix 11
Patient Global Impression of Change for Fatigue

Over the last 6 months, my fatigue is (please tick one box):

☐ Very much better

☐ Much better

☐ A little better

☐ The same

☐ A little worse

☐ Much worse

☐ Very much worse

Appendix 12
Patient Global Impression of Change for Upper Limb Function

Some people with MS have problems with their hands and arms (e.g., weakness, stiffness, or numbness in fingers). These problems can make it difficult to do everyday tasks (e.g., doing up buttons, using cutlery, carrying a heavy box, or taking a book off a high shelf).

Over the last 6 months, how has your ability to do tasks involving your arms/hands changed? (please tick a box):

☐ Very much better

☐ Much better

☐ A little better

☐ The same

☐ A little worse

☐ Much worse

☐ Very much worse

Appendix 13
Pregnancy Outcome and Infant Health Information on First Year of Life

Pregnancy Outcome and Infant Health Information on First Year of Life

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

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

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

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

Table 2: Information on birth

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

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Table 3: Growth alteration, congenital anomalies and functional deficits

Date of Assessment			
Growth alteration - Yes ☐ - No ☐	☐Small for gestational age (SGA) ☐Low birth weight ☐Short birth length	If Growth alteration present: Specify weight:_____ Specify length: _____	Contributing factors:
Congenital anomalies - Yes ☐ - No ☐	☐ Major structural malformation A defect that has either cosmetic or functional significance to the child	Specify: _____ _____	Contributing factors:
	☐ Minor structural malformation A defect that occurs infrequently but has neither cosmetic nor functional significance to the child	Specify: _____ _____	
	☐ Deformation A defect attributable to deformation of a structure, which had previously formed normally (usually due to mechanical force)	Specify: _____ _____	
	☐ Disruption A defect due to destruction of a structure, which has previously formed normally (may be of vascular, infectious, or mechanical origin)	Specify: _____ _____	
Functional deficit (except for infections, which should be described in separate table below) - Yes ☐ - No ☐	☐Functional deficit	Specify: _____ _____ _____	Contributing factors: _____ _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

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

Table 4: Status of infant

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

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes
☐ No
☐ Unknown

If infection detected at birth then Tables 5 and 6 should to be filled out and additional detailed information may be provided on last page.

If no infection detected at birth, however an infection developed later during the first year of live, please move directly to Table 7.

If no infection detected at birth, and if also no infection developed during the first 12 months then move directly to Table 8.

Table 5: Information on infection in neonate at birth

Specify the event term:	**Event number**		
Location of infection present in neonate at birth? Site of infection (specify):		**Outcome of infection?**	**Duration of infection?**
		☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration**:_____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti-infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No	☐Yes, specify: _____ ☐No
☐Life-threatening (Grade 4) ☐Death (Grade 5)		☐Unknown	☐Unknown
Relevant laboratory test results (in newborn infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

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

Maternal risk factors for neonatal infection	**Date of diagnosis**	If **diagnosed, was pregnant mother treated with anti-infective prior to delivery?**
☐Maternal intrapartum colonization or infection with group B streptococcus (GBS) ☐Maternal listeriosis ☐Premature rupture of membranes (PROM) ☐Meconium in amniotic fluid (meconium-stained liquid) ☐Active genital herpes infection ☐CMV ☐HPV (papilloma virus) Other, specify	_____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____

Relevant laboratory test results in pregnant mother:			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify: (e.g., any specific antibodies and their titers)	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

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

☐ Yes
☐ No
☐ Unknown

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

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

Specify the event term:	**Event number (automatically populated by the system?)**		
Location of infection?	**Infant's age on day of onset of infection?**	**Outcome of infection?**	**Duration of infection?**
Site of infection (specify): _____ _____	**Age:** _____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	**Duration:**_____
Intensity of infection (Grade 1-5 NCI CTCAE)?	**Seriousness of infection?**	**Treatment with anti- infective?**	**Pathogen causing infection known?**
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

Appendix 13: Pregnancy Outcome and Infant Health Information on First Year of Life (cont.)

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

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐Hemophilus influenza type b			
☐Pneumococcal			
☐Poliovirus ☐Attenuated oral polio vaccine ☐Inactivated polio vaccine			
☐Meningococcal group B bacteria			
☐Tuberculosis (Bacille Calmette Guérin, BCG) bacteria			
☐Other vaccination, specify: _____			

Table 9: Fetal/neonatal abnormalities in previous pregnancies

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

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

Please enter text in the free text box below.

Appendix 14
Investigational and Auxiliary Medicinal Product Designations for use in European Economic Area and United Kingdom

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Ocrelizumab	*IMP (test product)*[a]	*Authorized*	*No*[b]
Ocrelizumab-matched placebo	*IMP (placebo)*	*Not authorized*	*Not applicable*
Methylprednisolone	*AxMP (Premedication)*	*Authorized*	*Yes*
Antihistamine (e.g. diphenhydramine)	*AxMP (Premedication)*	*Authorized*	*Yes*
Analgesic/antipyretic (e.g. acetaminophen)	*AxMP (Premedication)*	*Authorized*	*Yes*

AxMP = auxiliary medicinal product; EEA =European Economic Area; IMP =investigational medicinal product.

[a] *Ocrelizumab is considered to be an IMP test product as well as an IMP comparator.*

[b] *Ocrelizumab is approved for the treatment of PPMS at a dose of 600 mg but not at the higher dose of 1200 mg (patient's body weight < 75 kg at baseline) or 1800 mg (patient's body weight ≥ 75 kg at baseline)*

Appendix 14: Investigational and Auxiliary Medicinal Product Designations for use in European Economic Area and United Kingdom (cont.)

Table 2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in U.K.*	*Used within Marketing Authorization*
Ocrelizumab	*IMP (test product)*[a]	*Authorized*	*No*[b]
Ocrelizumab-matched placebo	*IMP (placebo)*	*Not authorized*	*Not applicable*
Methylprednisolone	*NIMP (Premedication)*	*Authorized*	*Yes*
Antihistamine (e.g. diphenhydramine)	*NIMP (Premedication)*	*Authorized*	*Yes*
Analgesic/antipyretic (e.g. acetaminophen)	*NIMP (Premedication)*	*Authorized*	*Yes*

IMP =investigational medicinal product; NIMP =non-investigational medicinal product.

[a] *Ocrelizumab is considered to be an IMP test product as well as an IMP comparator.*

[b] *Ocrelizumab is approved for the treatment of PPMS at a dose of 600 mg but not at the higher dose of 1200 mg (patient's body weight < 75 kg at baseline) or 1800 mg (patient's body weight ≥ 75 kg at baseline)*

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