Official Title: A Phase IIIB, Multicenter, Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a Higher Dose of Ocrelizumab in Adults with Relapsing Multiple Sclerosis

NCT Number: NCT04544436

Document Date: Protocol Amendment Version 4: 21-Dec-2023

PROTOCOL

PROTOCOL TITLE:	A PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	BN42082
VERSION NUMBER:	4
TEST PRODUCT:	Ocrelizumab (RO4964913)
STUDY PHASE:	Phase IIIB
REGULATORY AGENCY IDENTIFIERS:	EU CT Number: 2023-506467-34-00 EudraCT Number: 2020-000893-69 IND Number: 100593 NCT Number: NCT04544436
SPONSOR'**S** NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124, 4070 Basel, Switzerland
APPROVAL	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	Date Final	Country	Version	Date Final
4	See electronic date stamp on the final page of this document			
3	27 October 2021	—	—	—
2	29 March 2021	—	—	—
1	19 May 2020	UK	1	11 September 2020

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BN42082 has been amended primarily to update the secondary and exploratory endpoints, clarify the timing of the end of the double-blind treatment (DBT) phase/decision to start the open-label extension (OLE), and to align with E.U. Clinical Trial Regulations (CTR) requirements. Changes to the protocol, along with a rationale for each change, are summarized below:

- Secondary and exploratory efficacy objectives have been updated as follows to reflect the current planned analyses, based on the latest understanding of the contribution of different endpoints to characterize the treatment effect of higher dose ocrelizumab (Sections 2.1.2 and 2.1.3). Note: these changes impact data analysis only and not study conduct:
    - Reclassification of the following endpoints from exploratory to secondary "Time to 8-point increase in 12 Item Multiple Sclerosis Walking Scale (MSWS 12)" and "Time to onset of 12-week composite confirmed disability progression (cCDP12) independent of protocol-defined relapses (PDR)" and addition of the following secondary endpoint "Time to onset of 48-week cCDP (cCDP48)"
    - Specification of the following secondary endpoints related to neurofilament light chain (NfL), in addition to those already described in Section 2.5 (Biomarker Objective): "Change in NfL (i.e. ratio to baseline) at Week 48 for patients assigned to the higher dose ocrelizumab group" and "Change in NfL (i.e., ratio to baseline) at Week 48 for patients assigned to the approved dose ocrelizumab group"
    - Reclassification of the following endpoints from secondary to exploratory "Time to onset of 24-week CDP (CDP24)", "Time to ≥ 20% increase in 24-week confirmed T25FWT", "Change from baseline in the Multiple Sclerosis Impact Scale 29 (MSIS 29) physical scale at Week 120"
- The secondary endpoint of MSWS-12 has been corrected to reflect that an *increase* in score indicates a worsening in walking ability (Section 2.1.2).
- Language has been added to clarify that the DBT Phase will continue, and investigators and patients will remain blinded and continue to receive blinded treatment, until the decision to start the OLE phase is communicated by the Sponsor (Sections 3.1, 3.1.1.2, 3.1.1.3 and 4.2.2).
- Table 6 has been added outlining the preparation and rates of infusion for the OLE (unblinded ocrelizumab 1200 mg or 1800 mg). To align the open-label infusion rates and as blinding considerations of the infusion procedure will no longer be required during the OLE phase, Bag 2 will be prepared at a concentration of 2.4 mg/mL in the 1200 mg arm as well as the 1800 mg arm (Section 4.3.2.1).
- A revised schedule for vital signs collection during the OLE phase has been added. During the OLE, ocrelizumab infusions will continue to be initiated and supervised by an experienced health care professional with access to appropriate medical support to manage severe reactions such as serious IRRs, if applicable. Intensive

collection of vital signs will be required only in the event of an IRR, otherwise specific timepoints will be collected (Section 4.5.6 and Appendix 2).

- The email address for withdrawal from the Research Biosample Repository after site closure has been updated (Section 4.5.11.6).
- Potential risks have been updated with current information about Progressive Multifocal Leukoencephalopathy (Section 5.1.1.2.1).
- The definition of Hy's law criteria has been updated to use the upper limit of normal as the reference value, which is aligned with the specific patient population in this study (Section 5.3.5.7).
- Text has been added to clarify that analyses will be performed as specified in the SAP (Section 6).
- A reference to the Clinical Trials Regulation has been added (Section 8.1).
- The website for information on the Roche Global Policy on Sharing of Clinical Study Information was updated (Section 9.6).

The protocol has also been amended to align with E.U. Clinical Trials Regulation (CTR) requirements. Changes related to E.U. CTR requirements have been made as follows:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitor has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 and in substudy Section 5.4.2 has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1 and substudy Section 5.2.4).
- The synopsis has been simplified to align with CTR and other guidelines in the main study and substudy.
- A section describing duration of participation has been added to align with CTR requirements (Section 3.2.1 and substudy Section 3.2.1).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 17).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).

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 NUMBER:	BN42082
VERSION NUMBER:	4
TEST PRODUCT:	Ocrelizumab (RO4964913)
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 as instructed by your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	A PHASE IIIb MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS
REGULATORY AGENCY IDENTIFIER NUMBERS:	EU CT Number: 2023-506467-34-00 EudraCT Number: 2020-000893-69 IND Number: 100593 NCT Number: NCT04544436

STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab in patients with relapsing forms of multiple sclerosis (RMS).

Exposure-response analyses of the pivotal Phase III studies in RMS and primary progressive multiple sclerosis(PPMS) in patients receiving the ocrelizumab 600 mg IV regimen showed a positive correlation between higher ocrelizumab exposure quartiles and the blood B-cell depletion levels. Moreover, higher exposure quartiles were associated with lower rates of confirmed disability progression (CDP) and the 12-week composite confirmed disability progression (cCDP) endpoint (including time to progression measured by the expanded disability status scale [EDSS], Timed 25-Foot Walk [T25FWT] or 9-Hole Peg Test [9-HPT]). Exposure-response relationships for safety parameters (serious adverse events [SAEs], serious infections, and infusion-related reactions [IRRs]) were also assessed, and no correlation between exposure quartiles and occurrence and grade of SAEs, serious infections, and IRRs was observed across both the RMS and PPMS populations.

In conclusion, based on efficacy and safety data across the exposure quartiles in patients with RMS and PPMS in the pivotal trials at a dose of 600 mg, it is expected that a higher dose of ocrelizumab could lead to an improved efficacy on disability progression, without compromising the patient safety as characterized in the MS studies of the 600 mg dose.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab in patients with RMS. Specific objectives and corresponding endpoints are outlined in the following table.

Primary Objective	Corresponding Endpoints
• To demonstrate the superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab as assessed by risk reduction in composite confirmed disability progression (cCDP) sustained for at least 12 weeks	Time to onset of cCDP, defined as the first occurrence of a confirmed progression event according to at least one of the following three criteria: • CDP, defined as a sustained increase from baseline in EDSS score of ≥ 1.0 point in patients with a baseline EDSS score of ≤ 5.5 or a sustained increase ≥ 0.5 points in patients with a baseline EDSS score of > 5.5, or • A sustained increase of ≥ 20% from baseline in T25FWT score, or • A sustained increase of ≥ 20% from baseline in time to complete the 9 HPT score.
Secondary Objectives	**Corresponding Endpoints**
• To demonstrate superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab	• Time to onset of 24-week cCDP (cCDP24) • Time to onset of 48-week cCDP (cCDP48) • Time to onset of cCDP12 independent of protocol-defined relapses (PDR), also termed progression independent of relapse activity (PIRA) as per Kappos et al. 2020 • Time to onset of 12-week CDP (CDP12) • Time to ≥ 20% increase in 12-week confirmed T25FWT • Annual rate of percent change from baseline in total brain volume • Time to 12-week confirmed 4-point worsening in Symbol Digit Modalities Test (SDMT) • Time to 12-week confirmed 8-point increase in 12-Item Multiple Sclerosis Walking Scale (MSWS-12)
• To demonstrate that both the higher dose and standard dose of ocrelizumab can significantly reduce NfL from baseline.	• Change in NfL (i.e. ratio to baseline) at Week 48 for patients assigned to the higher dose ocrelizumab group • Change in NfL (i.e ratio to baseline) at Week 48 for patients assigned to the approved dose ocrelizumab group
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety profile of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab	• Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 • Change from baseline in clinical laboratory test results (including hematology, chemistry, and Ig levels) • Change from baseline in vital signs (including systolic and diastolic blood pressure, and pulse rate) following study treatment administration

Pharmacokinetic/Pharmacodynamic Objectives	Corresponding Endpoints
• To assess the exposure to ocrelizumab in serum in all patients in both study arms	• Serum concentration of ocrelizumab at specified timepoints, and derived PK parameters via the population PK approach
• To characterize the ocrelizumab PD profile	• B-cell levels in blood (including comparing the degree of B-cell depletion between the doses) • Proportion of patients achieving 5 or less B-cells per microliter of blood • Proportion of patients achieving 5 or less B-cells per microliter of blood in patients with the high versus low affinity Fcγ Receptor 3A (FcγR3A) genotype per arm
Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to ocrelizumab	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
Biomarkers Objective	Corresponding Endpoints
• To identify biomarkers that are predictive of response to a higher dose of 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., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Levels of soluble biomarkers including but not limited to neurofilament light chain (NfL) and/or IL-6 in blood (plasma and/or serum) • Levels of blood B-cells based on a highly sensitive assay (MRB1.1) that can accurately measure below 5 B-cells per microliter in blood • Levels of B or T-cell subsets in blood, including but not limited to CD19+ IgD, CD27, CD38, CD4, CD8, CD3, parameters to identify B or T naive, memory and/or B plasmablast/plasma cell subsets • DNA genotype of patients to include but not be limited to FcγR3A and human leukocyte antigen (HLA) genotype. Collection and submission of blood samples for whole genome sequencing (WGS) or whole exome sequencing (WES) is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 2.

OVERALL DESIGN AND STUDY POPULATION

Study BN42082 is a Phase IIIb, randomized, double-blind, controlled, parallel group, multicenter study to evaluate efficacy, safety and pharmacokinetics of a higher dose of ocrelizumab in patients with RMS, in comparison to the approved dose of ocrelizumab.

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

Phase:	Phase IIIb	Population Type:	Adult patients
Control Method:	Active comparator	Population Diagnosis or Condition:	RMS
Interventional Model:	Parallel group	Population Age:	18-55 years
Test Product{s}:	Ocrelizumab	Site Distribution:	Multi-site
Active Comparator:	Ocrelizumab	Study Treatment Assignment Method:	Randomization
Number of Arms:	2	Number of Participants to Be Enrolled:	Approximately 786

STUDY TREATMENT

All eligible patients will be randomized 2:1 in a blinded fashion to either ocrelizumab higher dose (1200 mg [patient's body weight < 75 kg at baseline] or 1800 mg [patient's body weight ≥ 75 kg at baseline]) or the approved dose (600 mg) of ocrelizumab administered per IV infusion every 24 weeks. Randomization will be performed through an interactive voice or web-based response system (IxRS). Approximately 786 patients will be enrolled and will be recruited globally. Patients who discontinue study medication early or discontinue from the study will not be replaced.

DURATION OF PARTICIPATION

The duration of study participation for an individual including screening, the blinded treatment phase, the OLE phase and safety follow-up (SFU) is expected to be approximately up to 7.5 years, depending on when they are randomized into 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 life
AE	adverse event
AESI	adverse event of special interest
ARR	annualized protocol-defined relapse rate
AxMPs	*Auxiliary medicinal products*
BCM	B-cell monitoring
cCDP	composite confirmed disability progression
cCDP12	12-week composite confirmed disability progression
cCDP24	24-week composite confirmed disability progression
CDP	confirmed disability progression
CDP12	12-week confirmed disability progression
CDP24	24-week confirmed disability progression
cIDP	composite initial disability progression
ClinRO	clinician reported outcome
C_{max}	maximum concentration observed
C_{mean}	average concentration observed
CNS	central nervous system
COA	Clinical Outcome Assessment
COVID-19*	coronavirus disease-2019
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBT	double-blind treatment
DMC	Data Monitoring Committee
DMT	disease-modifying therapy
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDC	electronic data capture
EDSS	expanded disability status scale
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimension Questionnaire
FDA	U.S. Food and Drug Administration
FS	functional system
FSH	follicle stimulating hormone
FSS	functional system score
Gd	gadolinium
HBcAb	hepatitis B core antibody

Abbreviation	Definition
HBcAg	hepatitis B core antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
iDMC	independent data monitoring committee
IE	intercurrent event
IFN	interferon
IMP	investigational medicinal product
IND	investigational new drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
LoE	lack of efficacy
LPLV	last patient, last visit
MFIS	modified fatigue impact scale
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSIS-29	multiple sclerosis impact scale-29
MSWS	multiple sclerosis walking scale
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-QoL	Quality of Life in Neurological Disorders
NfL	neurofilament light
NIMP	non-investigational medicinal product
OCB	oligoclonal bands
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PDR	protocol-defined relapse
PerfO	performance outcomes
PGI-C	patient global impression of change
PGI-C-UL	patient global impression of change of upper limb function
PGI-S	patient global impression of severity
PIRA	*progression independent of relapse activity*
PK	pharmacokinetic
PML	*progressive multifocal leukoencephalopathy*
PMS	progressive multiple sclerosis
PPMS	primary progressive multiple sclerosis
PRO	patient-reported outcome
RA	rheumatoid arthritis

Abbreviation	Definition
RAW	relapse associated worsening
RBC	red blood cell
RBR	research biosample repository
RMS	relapsing multiple sclerosis
ROW	rest of world
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2*	severe acute respiratory syndrome coronavirus 2
SDMT	Symbol Digit Modalities Test
SFU	safety follow-up
SIE	serious infection
SoA	schedule of activities
SOC	system organ class
SPMS	secondary progressive multiple sclerosis
T1Gd+	gadolinium-enhancing lesions on T1-weighted
T25FWT	timed 25-foot walk test
ULN	upper limit of normal
VAS	Visual Analog Scale
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing

* The terms SARS-CoV-2 and COVID-19 are used interchangeably in relation to vaccination in the document.

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 2.8 million worldwide (MSIF 2020). It is primarily a disease of young adults, with patients usually being diagnosed between the ages of 20 and 40 (Calandri et al. 2019), and a mean age of diagnosis of approximately 30 years (GBD 2016). Multiple sclerosis has a gender bias influenced by the phenotype, with approximately twice as many females with MS as there are males (Goodkin 2014; MSIF 2020).

Multiple sclerosis is a serious, disabling disease, which is the leading medical cause of acquired neurological disability in young adults (Hauser and Oksenberg 2006; Tullman 2013). The clinical signs in MS can occur in isolation or in combination, and can include muscle weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasescu et al. 2014).

MS is classified into three clinical phenotypes: relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS) (Lublin et al. 2014). These three phenotypes are further subdivided into active and non-active forms based on the presence or absence of disease activity, defined by the presence of clinical relapses and/or so-called active lesions on a magnetic resonance imaging (MRI) scan. Active MRI lesions are gadolinium-enhancing lesions on T1-weighted scan (T1Gd+), or new/enlarging T2-weighted lesions. The term Relapsing MS (RMS) comprises both RRMS and early stages of SPMS where patient still experience relapses (Lublin et al. 2014).

Evidence available to date suggests that despite the potential heterogeneity of the clinical expression of the disease, PPMS, SPMS, and RRMS belong to the same disease spectrum, and that pathological mechanisms responsible for relapses/disease activity and progression biology are largely identical across the MS spectrum (Lassmann 2018). Although the mechanisms associated with disease progression are assumed to be present from the onset of the disease (Cree et al. 2019), clinical disability progression manifests often later in the course of a patient's disease most likely due to the degree of brain reserve of the patient. The symptomatic worsening associated with MS disability progression results in a slow, insidious loss of a patient's motor and sensory function, as well as cognitive decline and autonomic dysfunctions (Lassmann 2018).

Disability progression across the spectrum of MS might occur as a result of two concurrent inflammatory mechanisms: acute inflammation and chronic compartmentalized inflammation.

Acute inflammation can be observed on a MRI scan (as T1Gd+ lesions or new/enlarging T2 lesions) and clinically manifests as relapses, where it can also lead to step-wise increase of disability due to incomplete relapse recovery. Pathophysiologically, relapsing forms of MS (i.e., RMS) are associated with focal T-cell and B-cell invasion, with blood brain barrier leakage that give rise to classic active demyelinating plaques in the white matter. However, RMS also harbors signs of progression biology/chronic compartmentalized inflammation.

By contrast to these acute inflammatory processes, chronic compartmentalized inflammation is responsible for an increase in disability that occurs independently from relapses or radiological disease activity and is characterized by demyelination and axonal loss (progression biology; Lassmann 2019). Progressive forms of MS (i.e., PMS) are associated with a chronic and slow accumulation of T cells and B cells in the connective tissue spaces of the brain, without leakage of the blood brain barrier. There is a typical formation of subpial-demyelinated lesions in the cerebral and cerebellar cortex, with slow expansion of pre-existing lesions in the white matter and diffuse chronic inflammation in the normal appearing white or gray matter (Lassmann 2019).

Even though there are many drugs currently available that target the acute inflammatory mechanisms associated with relapses and relapse associated worsening, to date, only ocrelizumab is indicated for PPMS (note: ocrelizumab is only approved for active PPMS [aPPMS] in some countries). As a result, the salient feature of disability progression in all forms of MS remains to be further addressed, and treatments that can stop or delay MS disease progression represent a serious unmet medical need.

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 pre-existing 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 RMS and PPMS, ocrelizumab was approved by the U.S. 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 of ocrelizumab 600 mg versus interferon β-1a in patients with RMS (Hauser et al. 2017); one randomized placebo-controlled study (ORATORIO [Study WA25046]) has demonstrated superior efficacy of ocrelizumab 600 mg 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 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 at least one 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]). Analysis of the data from open-label extension (OLE) of the pivotal studies supported the long-term consistency of benefit–risk (Hauser et al. 2019).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Ocrelizumab is indicated for use in the RMS and PPMS populations at an approved dose of 600 mg every 6 months, with demonstrated reduction in disease activity and disability progression.

Higher dose of ocrelizumab will be tested in the relapsing and primary progressive MS populations (studies BN42082 and BN42083, respectively). Study rationale for testing a higher dose of ocrelizumab in patients with RMS and PPMS is based on (1) exposure-response analyses in the pivotal Phase III studies in RMS and PPMS, (2) data from the Phase II study in RRMS which included a higher dose of 2000 mg ocrelizumab, and (3) data from previous Phase I to III studies with higher doses of ocrelizumab in rheumatoid arthritis (RA) i.e., 1000 mg, 1500 mg, and 2000 mg.

1.3.1 Exposure-Response Analyses of Pivotal Studies in RMS and PPMS

In the Phase III pivotal studies with ocrelizumab 600 mg in patients with RMS (WA21092/WA21093) and PPMS (WA25046), a positive correlation between ocrelizumab exposure quartiles and the blood B-cell depletion level was observed. Moreover, higher exposure quartiles were associated with lower rates of CDP. Namely, for the 12-week CDP outcome, those in the highest exposure quartile were estimated to have a hazard ratio of 0.33 (95% CI: 0.17, 0.64) and 0.59 (95% CI: 0.40, 0.86) versus interferon (IFN) and placebo for patients with RMS and PPMS, respectively. In comparison, those in the lowest exposure quartile were estimated to have a hazard ratio of 0.77 (95% CI: 0.49, 1.21) and 0.87 (95% CI: 0.60, 1.27) versus IFN and placebo for patients with RMS and PPMS, respectively. Similarly, greater risk reductions for patients with higher exposure were also observed in the 12-week composite confirmed disability progression (cCDP) endpoint. Composite CDP included time to progression measured by the expanded disability status scale (EDSS), Timed 25-Foot Walk (T25FWT) or

9–Hole Peg Test (9-HPT). Those in the highest exposure quartile were estimated to have a hazard ratio of 0.50 (95% CI: 0.35, 0.72) and 0.69 (95% CI: 0.52, 0.90) versus IFN and placebo for patients with RMS and PPMS, respectively. In comparison, those in the lowest exposure quartile were estimated to have a hazard ratio of 0.80 (95% CI: 0.58, 1.10) and 0.84 (95% CI: 0.64, 1.11) versus IFN and placebo for patients with RMS and PPMS, respectively. In addition, an exploratory analysis based on predicting treatment effects suggests that the higher dose regimen proposed in this study will achieve greater risk reduction on progression endpoints in comparison to the approved dose of 600 mg. Appendix 16 provides more details of this exploratory analysis.

At the same time, exposure-response relationships for safety parameters (serious adverse events, serious infections, and infusion-related reactions [IRRs]) were also assessed, and no correlation between exposure quartiles and occurrence and grade of SAEs, serious infections, and IRRs was observed in patients receiving the ocrelizumab 600 mg IV regimen across both the RMS and PPMS populations (Table 11A-1 and Table 11A-2 in Appendix 11).

Furthermore, the maximum concentrations observed (C_{max}) for ocrelizumab were not higher in patients that experienced at least one SAE compared with patients without SAEs, at the 600 mg dose. For both RMS and PPMS, the graphical analysis of the occurrence of SAE by system organ class (SOC) in patients treated with ocrelizumab showed no dependencies on exposure.

In conclusion, based on efficacy and safety data across the exposure quartiles in patients with RMS and PPMS in the pivotal trials at a dose of 600 mg, it is expected that a higher dose of ocrelizumab could lead to an improved efficacy on disability progression, without compromising the safety profile of the drug as characterized in the MS studies of the 600 mg dose.

1.3.2 Pharmacokinetics and Safety Analysis of the Phase II Study in RRMS

In the Phase II RRMS Study WA21493 (Section 3.3.1), patients were randomly assigned to either placebo, 600 mg, or 2000 mg of ocrelizumab, administered as two infusions of 300 mg or 1000 mg given 15 days apart. The 2000 mg dose of ocrelizumab was only given for Cycle 1, followed by single 1000 mg infusions for the subsequent dosing occasions. Overall, the study showed a favourable safety profile for both the 600 mg and 2000 mg dose of ocrelizumab (details are provided in Appendix 11). The pharmacokinetic (PK) analyses of the Phase II study data were also used to set the criterion for the highest ocrelizumab exposure to be tested in this study; an observed average concentration over the treatment period (C_{mean}) of 83 µg/mL was well tolerated in patients who received 2000 mg ocrelizumab. The intended dose in Study BN42082 will keep 99% patients below the C_{mean} of 83 µg/mL, as predicted by the population PK model.

The safety profiles of the 600 mg and 2000 mg doses were similar, except for IRR rate which was higher at first infusion in the 2000 mg arm compared to the 600 mg arm (44% vs. 35%). Most of IRRs at first infusion were mild to moderate (100% of IRRs for ocrelizumab 600 mg and 95.8% for ocrelizumab 2000 mg). The percentage of patients experiencing an IRR was lower after the second infusion (Day 15). In order to reduce potential infusion reactions, patients in the Phase II study received prophylactic treatment with methylprednisolone 100 mg. Pre-infusion treatment with an oral analgesic/antipyretic (e.g., acetaminophen), and an oral antihistamine (e.g., diphenhydramine) were proposed as recommendation only. As proven in the subsequent studies, the addition of oral antihistamine to methylprednisolone pre-treatment for each infusion was associated with a lower incidence overall in IRRs compared with pre-treatment with methylprednisolone alone. Mandatory antihistamine is also included in Study BN42082.

1.3.3 Safety of Higher Doses of Ocrelizumab in Rheumatoid Arthritis

The pooled analyses (N=3322) of safety data from the Phase III studies of 400 mg (N=1186) and 1000 mg (N=947) ocrelizumab in RA showed no correlation between exposure and safety findings, except for infections and serious infections. Serious infections were reported more frequently in the 1000 mg arm compared to the 400 mg arm. Risk factors for developing serious infections in these trials included other comorbidities, chronic concomitant use of steroids/immunosuppressants (including leflunomide and methotrexate), and patients from Asia. When adjusting the rates of serious infections in RA for various risk factors (i.e., geographical region, gender, age, use of steroids and/or methotrexate, and levels of IgM and neutrophils) and predicting the rates of serious infections in MS population with baseline characteristics as observed in the OPERA studies (such as younger average age, no use of steroids or methotrexate, no patients from Asia), no dose dependent increase in serious infections rate in MS population up to 1000 mg is expected (Figure 11A-1 in Appendix 11).

1.3.4 Summary of the Study Rationale and Benefit–Risk Assessment

Exposure-response analyses of the pivotal Phase III studies in RMS and PPMS showed that higher exposure quartiles were associated with lower rates of CDP without compromising the safety profile of the drug.

Exposure and safety data from the Phase II study in RRMS which included the dose of 2000 mg of ocrelizumab, and data from previous Phase I to III studies with higher doses of ocrelizumab in RA (i.e., 1000 mg, 1500 mg, and 2000 mg) suggested that higher doses of ocrelizumab should not impact significantly the safety profile of the drug in MS patients. This study will evaluate efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab (1200 mg [for patients with a body weight $<$ 75 kg at baseline] or 1800 mg [for patients with a body weight $\geq$ 75 kg at baseline]) per IV infusion every 24 weeks. By weight adjusting the higher dose in this study, it is expected that $<$ 1% of the study participants would have an exposure higher than the exposure previously observed with

2000 mg (i.e., $C_{mean} > 83$ µg/mL). Based on the previous experience with higher doses of ocrelizumab, ocrelizumab MS Phase II/III exposure-safety correlation, the statistical modeling and prediction of Serious Infections (SIE) rates in MS population from the RA data, the higher dose of 1200 mg and 1800 mg are expected to be well tolerated.

In conclusion, it is expected that higher doses of ocrelizumab will provide greater benefit for patients in further reducing CDP, without compromising the safety profile of the drug.

1.3.5 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 the 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 COVID-19 follows a similar course in these patients as in the general population, with risk factors for severe COVID-19 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 COVID-19 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 COVID-19, 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 retreatment with ocrelizumab.

A higher dose of ocrelizumab is expected to provide greater benefit for patients in controlling MS progression compared with the approved dose. 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 the ocrelizumab retreatment criteria are considered adequate in the context of conducting the study during the COVID-19 pandemic. Investigators should manage COVID-19 in the same way as infections caused by any other pathogen, as per local guidelines.

1.3.6 Benefit–Risk Assessment For Concomitant Use of a COVID-19 Vaccine

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

vaccines on the conduct of this study. Based on this assessment, no interaction between the concomitant use of SARS-CoV-2 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 [Section 4.4.4], and impaired response to vaccination [Section 5.1.1.1.3]), safety monitoring, and risk mitigation measures related to administration of vaccines (including those for SARS-CoV-2) are considered adequate.

As described in Section 5.1.1.1.3 (impaired response to vaccination), data from the pivotal Phase III studies of ocrelizumab in RMS and PPMS show that pre-existing 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 people with MS treated with ocrelizumab were able to mount a humoral immune response to non-live vaccines and new antigens. The antibody immune response was considered protective, albeit with reduced levels of antibodies compared to controls. In that study, 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.

Roche is continually collecting evidence from clinical and biological sources to better understand immune response mechanisms of the SARS-CoV-2 vaccine in ocrelizumab-treated patients. Please refer to Sections 2.7, 3.3.6, 4.5.12, and 6.10 for details on the exploratory vaccine immune response objective for this study.

As with any other medication or vaccine, SARS-CoV-2 vaccines should be reported as concomitant medication by using the standard fields in the clinical database (see immunizations [Section 4.4.4], and medical history, baseline conditions, concomitant medications, and demographic data [Section 4.5.2]).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab in patients with relapsing forms of MS. 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 is to demonstrate the superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab as assessed by risk reduction in cCDP sustained for at least 12 weeks.

The comparison of interest is the difference in time to 12-week cCDP (cCDP12), as expressed by the hazard ratio. The primary comparison will be made regardless of adherence to the randomized treatment or use of an approved MS disease-modifying therapy (DMT) medication.

Time to onset of cCDP is defined as the first occurrence of a confirmed progression event according to at least one of the following three criteria:

- CDP, defined as a sustained increase from baseline in EDSS score of ≥1.0 point in patients with a baseline EDSS score of ≤5.5 or a sustained increase ≥0.5 points in patients with a baseline EDSS score of >5.5, or
- A sustained increase of ≥20% from baseline in T25FWT score, or
- A sustained increase of ≥20% from baseline in time to complete the 9-HPT score.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective is *twofold. First,* to demonstrate superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab on the basis of the following endpoints:

- Time to onset of 24-week cCDP (cCDP24)
- *Time to onset of 48-week cCDP (cCDP48)*
- Time to onset of cCDP12 independent of protocol-defined relapses (PDR), *also termed progression independent of relapse activity (PIRA) as per Kappos et al 2020*
- Time to onset of 12-week CDP (CDP12)
- Time to ≥20% increase in 12-week confirmed T25FWT
- Annual rate of percent change from baseline in total brain volume
- Time to 12-week confirmed 4-point worsening in Symbol Digit Modalities Test (SDMT)
- Time to *12-week confirmed* 8-point *increase* in 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

Second, to demonstrate that both the approved dose and the higher dose of ocrelizumab can lead to a significant reduction in NfL from baseline by evaluating the following endpoints:

- *Change in NfL (i.e. ratio to baseline) at Week 48 for patients assigned to the higher dose ocrelizumab group*
- *Change in NfL (i.e ratio to baseline) at Week 48 for patients assigned to the approved dose ocrelizumab group*

For all time to event endpoints, the comparison of interest is the difference in time to event between treatment arms, as expressed by the hazard ratio.

For all other endpoints*, with the exception of the NfL endpoints*, the comparison of interest is the difference in variable means between treatment arms. *For the NfL endpoints, the comparisons are the change from baseline at Week 48 within each treatment arm. This analysis aims to demonstrate that both the approved dose and the higher dose of ocrelizumab can lead to a significant reduction in NfL from baseline.*

All comparisons, except for the MRI *and NfL* endpoint*s* (*e.g.*, the change in brain volume), will be made regardless of adherence to the randomized treatment or use of an approved MS DMT medication. For the MRI *and NfL* endpoint*s*, the comparison will be made as if no treatment discontinuation or switch to an approved MS DMT medication had occurred.

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab on the basis of, but not limited to, the following endpoints:

- Change from baseline in EDSS score at each scheduled visit
- Time to onset of 24-week CDP (CDP24)
- Time to ≥20% increase in 24-week confirmed T25FWT
- Time to≥20% increase in 12-week confirmed 9-HPT
- Time to≥20% increase in 24-week confirmed 9-HPT
- The following patient-reported outcomes:
    - Change from baseline in the Multiple Sclerosis Impact Scale-29 (MSIS-29) physical scale at *each scheduled visit*
    - Change from baseline in MSIS-29 psychological scale at each scheduled visit
    - Change from baseline in Quality of Life in Neurological Disorders (Neuro-QoL) Upper Extremity Function Form at each scheduled visit
    - Change from baseline in Modified Fatigue Impact Scale (MFIS) at each scheduled visit
    - Proportion of patients with no change, improvement or worsening, in patient global impression of severity (PGI-S) at each scheduled visit
    - Proportion of patients with no change, improvement or worsening, in patient global impression of change (PGI-C) at each scheduled visit
    - Proportion of patients with no change, improvement or worsening, in patient global impression of change of the upper limb function (PGI-C-UL) at each scheduled visit
- Time to onset of progression in cCDP individual components independent of protocol-defined relapses (PDR)
- Total number of new T1-hypo-intense lesions (black holes)
- Volume of T1-hypo-intense lesions (black holes)

- Volume of spinal cord (upper part of the spine)
- Annualized protocol-defined relapse rate (ARR)
- Time to onset of 12-week confirmed protocol-defined relapse associated worsening (RAW) and individual components
- Total number of new or enlarging T2 lesions per MRI scan over the 120-week treatment period and at each scheduled visit
- Total number of T1Gd+ lesions over the 120-week treatment period and at each scheduled visit

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety profile of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab as well as the overall safety profile and safety profile by treatment arm over time, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0
- Change from baseline in clinical laboratory test results (including hematology, chemistry, and Ig levels)
- Change from baseline in vital signs (including systolic and diastolic blood pressure, and pulse rate) following study treatment administration

2.3 PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

The PK objective for this study is to assess the exposure to ocrelizumab in serum in all patients in both study arms:

- Serum concentration of ocrelizumab at specified timepoints, and derived PK parameters via the population PK approach

The exploratory PK objectives for this study are to evaluate a potential relationship between drug exposure and the efficacy and safety of ocrelizumab:

- Correlation of ocrelizumab serum concentration with efficacy endpoints
- Correlation of ocrelizumab serum concentration with safety endpoints

The pharmacodynamic (PD) objective for this study is to characterize the ocrelizumab PD profile on the basis of the following endpoints:

- B-cell levels in blood (including comparing the degree of B-cell depletion between the doses)
- Proportion of patients achieving 5 or less B-cells per microliter of blood
- Proportion of patients achieving 5 or less B-cells per microliter of blood in patients with the high versus low affinity Fcγ Receptor 3A (FcγR3A) genotype per arm

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to ocrelizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The relationship between ADA status and pharmacokinetics, pharmacodynamics, efficacy, and safety may also be explored.

2.5 BIOMARKER OBJECTIVE

The biomarker objectives for this study are to identify biomarkers that are predictive of response to a higher dose of 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., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety. The following biomarker analyses may be implemented:

- Levels of soluble biomarkers including but not limited to neurofilament light chain (NfL) and/or IL-6 in blood (plasma and/or serum)
- Levels of blood B-cells based on a highly sensitive assay (MRB1.1) that can accurately measure below 5 B-cells per microliter in blood
- Levels of B or T-cell subsets in blood, including but not limited to CD19+ IgD, CD27, CD38, CD4, CD8, CD3, parameters to identify B or T naive, memory and/or B plasmablast/plasma cell subsets
- DNA genotype of patients to include but not be limited to FcγR3A and human leukocyte antigen (HLA) genotype. Collection and submission of blood samples for whole genome sequencing (WGS) or whole exome sequencing (WES) is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

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 a higher dose of ocrelizumab compared with the approved dose of ocrelizumab on the basis of the following endpoint:

- Change from baseline at each scheduled visit in EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index score and clinical measurements that may support pharmacoeconomic modeling

2.7 EXPLORATORY COVID-19 VACCINE IMMUNE RESPONSE OBJECTIVE

The exploratory vaccine immune response objective for this study is to investigate the effect of a higher dose and of an approved dose of ocrelizumab on antibody and T-cell responses in patients administered with an approved or authorized COVID-19 vaccine. The following endpoints will be analyzed:

- SARS-CoV-2 antibody titers
- SARS-CoV-2 T-cell responses

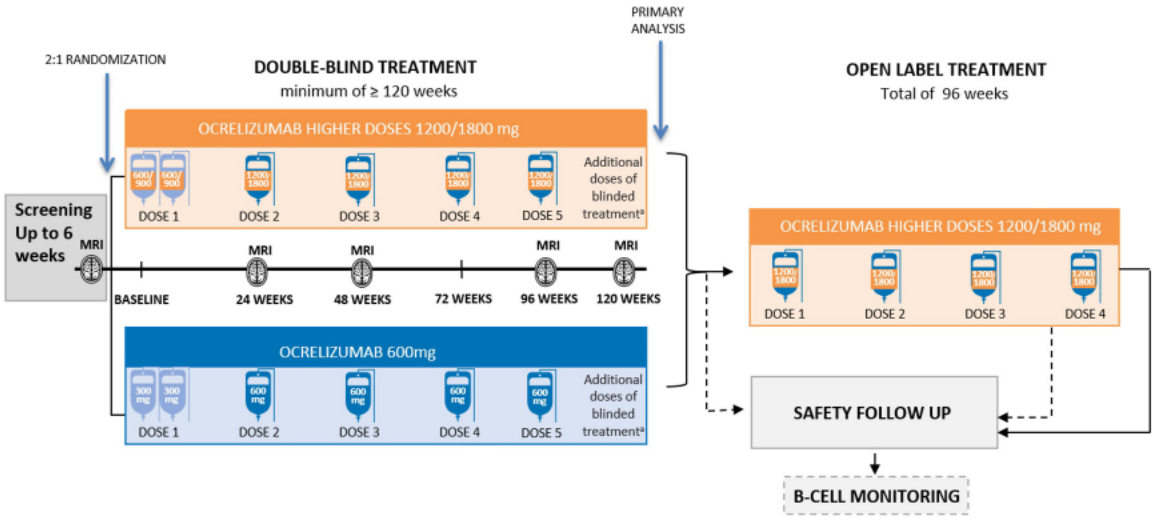
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study BN42082 is a Phase IIIb, randomized, double-blind, controlled, parallel group, multicenter study to evaluate efficacy, safety and pharmacokinetics of a higher dose of ocrelizumab (1200 mg [patient's body weight $<$ 75 kg at baseline] or 1800 mg [patient's body weight $\geq$ 75 kg at baseline]) per IV infusion every 24 weeks in patients with RMS, in comparison to the approved 600 mg dose of ocrelizumab. This study will consist of the following phases: screening, double-blind treatment (DBT) phase, open-label extension (OLE) phase, safety follow-up (SFU), and B-cell monitoring (BCM; see Section 3.1.1.4 for details).

Figure 1 presents an overview of the study design. Table 1 presents the overview of ocrelizumab dosing regimen during the DBT phase. The schedule of activities (SoA) are provided in Appendix 1, Appendix 2, and Appendix 3.

Figure 1 Study Design



cCDP12 = 12-week composite confirmed disability progression; MRI = magnetic resonance imaging.

[a] The double-blind treatment period will continue until the last patient completes at least 120 weeks (a minimum of 5 study drug doses with 24 weeks follow-up after 5th dose, with each dose 24 weeks apart) and the target number of cCDP12 events is reached, *the primary analysis is performed and the decision to start the OLE is communicated by the Sponsor.*

Table 1 Overview of Ocrelizumab Dosing Regimen During the Double-Blind Treatment Phase

	Double-Blind Treatment Phase						
	Minimum 5 Treatment Doses (120 Weeks) [a, b, c]						
	Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	N (additional treatment doses) [a] (Every 24 wks)
	Day 1	Day 15	Wk 24	Wk 48	Wk 72	Wk 96	Wk 120+
A OCR higher dose **patients <75 kg** [d]	600 mg	600 mg	1200 mg	1200 mg	1200 mg	1200 mg	1200 mg
A OCR higher dose **patients ≥75 kg** [d]	900 mg	900 mg	1800 mg	1800 mg	1800 mg	1800 mg	1800 mg
B OCR approved dose	300 mg	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg

cCDP12=12-week composite confirmed disability progression; DBT=double-blind treatment; IV=intravenous; OCR=ocrelizumab; Wk=week.

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

[a] Enrolled patients will undergo ocrelizumab (approved or higher dose) treatment of minimum of five treatment doses. When applicable, patients will have subsequent treatment dosing that will consist of the same dosing regimen, at 24-week intervals, until the end of the DBT period. The DBT period will end once the last patient completes at least 120 weeks (a minimum of five study drug doses with 24 weeks follow-up after 5th dose, with each dose 24 weeks apart) and the target number of cCDP12 events is reached*, the* primary analysis is performed *and the decision to start the OLE is communicated by the Sponsor*.

[b] After the first infusion of the first dose, an evaluation of retreatment criteria will be performed before each subsequent infusion to ensure the patient remains eligible for further treatment

[c] 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 infusions. In patients where methylprednisolone is contraindicated, equivalent doses of other IV steroids (e.g., dexamethasone) should be used as premedication.

[d] The actual higher dose of ocrelizumab will be assigned to patients as based on their body weight at baseline: 1200 mg (patient's body weight<75 kg) or 1800 mg (patient's body weight≥75kg).

3.1.1 Overview of the Study Phases

3.1.1.1 Screening

Patients providing informed consent will undergo screening prior to the study drug administration.

Procedures at screening will include collecting medical history, physical examination, MRI, PROs, complete neurological examination 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 screening phase lasting for up to 6 weeks, the investigator is required to verify that the patient still meets eligibility criteria prior to randomization.

Eligible patients will be randomized (2:1) in a blinded fashion to either the higher dose or the approved dose of ocrelizumab. Randomization will be performed through an interactive voice or web-based response system (IxRS).

The randomization will be stratified by weight at baseline (<75 kg or ≥75 kg), region (U.S. or Rest of World [ROW]), EDSS (<4.0 vs. ≥4.0) and age at screening (≤45 or >45).

The sample size will be approximately 786 patients (524 in the higher dose arm and 262 in the approved dose control arm).

The subtype of RMS (i.e., RRMS or [a]SPMS) will be collected at screening for each patient and recorded in the electronic Case Report Form (eCRF).

The actual higher dose of ocrelizumab will be assigned to patients as based on their body weight:

- 1200 mg ocrelizumab for patients with body weight <75 kg at baseline
- 1800 mg ocrelizumab for patients with body weight ≥75 kg at baseline

Throughout the study conduct, patients will continue to receive the dose assigned at baseline. Changes of the study drug dose assigned at baseline are not foreseen. Significant changes in patient's body weight during study should be reported as described in Section 5.3.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 90 days after previously signing the consent form, unless instructed otherwise by the Sponsor based on specific situations. The investigator will record reasons for screen failure in the screening log and in the eCRF. The re-screening process will be detailed in a separate document and sites will be trained accordingly.

3.1.1.2 Double-Blind Treatment Phase

This is an event-driven study. Patients will be treated for a minimum of 120 weeks (with a minimum of five study drug doses, with 24-week follow-up after fifth dose, with each dose 24 weeks apart) or longer and the blinded treatment will continue until at least 205 events of cCDP12 have occurred in the study. The primary efficacy analysis will be

performed after the above-mentioned number of events has been reached (in accordance to the definition of events for the primary estimand). Of note: each study dose period will last for 24 weeks, starting from the study drug dose administration.

Of note: Patients who prematurely discontinue from study treatment, including patients who start receiving an approved MS DMT medication, will remain in the main double-blind study phase and will be followed for both efficacy and safety until the end of the double-blind phase (i.e., until the time of the primary analysis).

Patients *and* investigators will remain blinded to the original (randomized) treatment allocation of patients who discontinued study treatment until the primary analysis is performed and *the decision to start the OLE phase is communicated by the Sponsor.*

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 of 22 weeks must occur between ocrelizumab single infusions administered during Weeks 24, 48, 72, 96, and any dose thereafter. *Minimum dosing intervals are to be used in exceptional circumstances only and visits should be scheduled according to the SoA outlined in* Appendix 1.

At infusion visits, patients should remain in observation for at least 1 hour after the completion of the infusion.

Treatment with the first study drug infusion should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the investigator assures that all inclusion and exclusion criteria are still met on the day of dosing). If for logistical reasons the ocrelizumab infusion at Week 24, 48, 72, 96, or any further infusion thereafter 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 (refer to Section 4.3.2.3). Whenever possible, infusion bags should be prepared on the day of the infusion administration.

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

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.

3.1.1.3 Optional Open-Label Extension Phase

Following database lock of the DBT, patients should continue to receive blinded treatment until the primary analysis is completed and the decision to start the OLE is

communicated by the Sponsor. If the result of the primary analysis is positive, an optional higher dose extension treatment (OLE phase) is planned for eligible patients who have adhered to the DBT until the primary analysis and, in the opinion of investigator, could benefit from a higher dose of ocrelizumab. The OLE will be carried out for approximately 96 weeks (4 doses in total) starting from the first OLE dose. The 96-week duration of the OLE phase serves to further evaluate long-term safety and efficacy of a higher dose of ocrelizumab (of note, the currently approved 600 mg dose of ocrelizumab will not be offered in this extension phase).

During the OLE phase, patients originally randomized to the higher dose group will continue with their assigned dose of ocrelizumab (either 1200 or 1800 mg). Patients who were assigned to the control group and received 600 mg ocrelizumab in the DBT, will be offered a higher dose of ocrelizumab, based on their body weight at OLE baseline.

The blinding procedures are not necessary during the OLE phase. All required assessments during the OLE phase should occur as described in OLE schedule of activities (see Appendix 2).

3.1.1.4 Safety Follow-Up Phase and B-Cell Monitoring

SFU phase will only begin after primary analysis results are available. Each patient will be followed for safety for 48 weeks, starting from the last ocrelizumab dose received.

Patients will either enter the SFU phase if they prematurely discontinued randomized treatment in the DBT phase but did not reach the 48-week follow-up post-study drug discontinuation within DBT phase by the time DBT phase ended, or if they completed or prematurely discontinued the OLE phase.

Patients who discontinue ocrelizumab treatment during the DBT phase will remain in the DBT phase until its conclusion and will continue to follow the DBT Schedule of Activities (refer to Section 3.1.1.2). This period of time within the DBT phase, where patients are not receiving an ocrelizumab infusion but are following the DBT Schedule of Activities, will count as part of the 48-week safety follow-up period. If these patients do not reach a 48-week period required for safety monitoring within the DBT phase, they will then transition to the SFU phase and will follow the SFU Schedule of Assessments.

Laboratory and safety assessments will be performed during the clinic visits that occur every 12 weeks.

At the end of the required safety follow-up (either within the DBT phase or the SFU phase), patients whose B-cell levels still did not replete to their baseline level or the low level of normal (LLN), whichever is lower, will move into the BCM phase. The study will end when all patients who were not treated with an alternative B-cell depleting

therapy have repleted their B-cells to the baseline value or the lower limit of normal (whichever is lower).

3.1.2 Optional CSF Biomarker Substudy

In the Ocrelizumab Biomarker Outcomes Evaluation Trial (OBOE; Study ML29966), it was reported that B-cells and NfL decrease in CSF in patients following treatment with ocrelizumab (Bar-Or et al. 2019). However, B-cells do not completely decrease in all patients. The purpose of this optional substudy is to assess whether higher doses of ocrelizumab have a greater impact on B-cell depletion in the CSF. The primary objectives of this substudy will assess NfL levels and B-cell number in the CSF. Secondary and exploratory objectives will assess the presence or absence of OCBs, the exposure of ocrelizumab, specific subsets or types of B-cells present, and T-cells or other biomarkers in the CSF. Patients consenting to the optional substudy will follow all main study procedures. In addition, substudy patients will undergo two lumbar punctures to obtain CSF as part of the substudy: pre-ocrelizumab at baseline and at Week 48 of the DBT. Patients will be asked to provide an additional optional sample at Week 24, but this is not required to participate in the substudy. The CSF biomarker substudy is currently expected to enroll up to 144 patients with RMS. For additional information on the substudy, see Appendix 18 .

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the DBT phase is defined as the date at which the last data point that is required for the primary efficacy analysis, as defined in the Statistical Analysis Plan (SAP), is received from the last patient.

The end of the study will occur when all patients, who are not being treated with an alternative B-cell depleting therapy, have repleted their B-cells (i.e., B-cell level of the patient has returned to the baseline value or the lower limit of normal, whichever is lower).

Because it is anticipated that it may take up to 2 years to recruit patients, the DBT phase may extend beyond 4.3 years for the initial group of patients enrolled in the study. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 7.5 years (6 weeks for screening, 226 weeks for blinded treatment phase [assuming that recruitment is completed in 2 years], followed by 96 weeks of OLE, 48 weeks of SFU, and a [variable] BCM phase).

In addition, the Sponsor may decide to terminate the study at any time (refer also to Section 4.7.3 for Study Termination by Sponsor).

3.2.1 *Duration of Participation*

The duration of study participation for an individual including screening, the blinded treatment phase, the OLE phase and SFU is expected to be approximately up to 7.5 years, depending on when they are randomized into the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ocrelizumab Dose and Schedule

The currently approved dosing regimen of ocrelizumab is 600 mg IV administered every 6 months. However, retrospective exposure-response analyses of the three pivotal Phase III studies (RMS [Study WA21092/WA21093] and PPMS [Study WA25046]) suggested that a higher dose of ocrelizumab may lead to improved efficacy (i.e., reduction in risk of disability progression), without compromising the safety profile of the drug, and this hypothesis will be assessed in this study.

The highest dose of ocrelizumab administered in previous MS studies was 2000 mg given as two infusions of 1000 mg 15 days apart in the Phase II RRMS study (WA21493). The C_{mean} reached with 2000 mg dose was 83 μg/mL.

The highest dose of ocrelizumab administered in this study will be 1200 mg IV every 24 weeks for patients with a body weight of $<$75 kg at baseline, and 1800 mg IV every 24 weeks for patients with a body weight $\geq$75 kg at baseline. The predicted C_{mean} of these weight-adjusted doses is below 83 μg/mL for $>$99% of patients. These doses are expected to be well tolerated, based on previous experience with higher doses of ocrelizumab (see details in Appendix 11), ocrelizumab MS Phase II/III exposure-safety correlation, statistical modeling and prediction of SIE rates in MS population from the RA data.

In order to improve efficacy (i.e., reduce the risk of disability progression), the target is to achieve in all patients in this study the ocrelizumab systemic exposure at which the best 12- and 24-week CDP outcomes were observed in the pivotal Phase III studies, i.e., C_{mean} of $>$22.2 μg/mL (RMS study) and $>$23.1 μg/mL (PPMS study). The population PK model built on the pivotal Phase III studies suggests that the higher dosing regimen is able to bring over 99% and 98% of the patients with RMS and PPMS to these exposure levels, while keeping over 99% of the patients with RMS and PPMS below a C_{mean} of 83 μg/mL.

To guide dose selection based on estimating minimum treatment effects, an exploratory analysis based on predicting efficacy of the higher dosing regimen was performed. Specifically, minimum treatment effects were predicted from weighted Cox models for time to 12-week cCDP with spline variables of C_{mean} as covariates. The Cox models were weighted to reduce the effects of confounding by baseline characteristics (e.g., BMI) on the C_{mean} effect on 12-week cCDP. The results of the exploratory analysis suggested that the higher dosing regimen will achieve greater risk reduction on progression endpoints in comparison to the approved dose of 600 mg. The summary of the exploratory analysis is presented in Appendix 16 .

3.3.2 Rationale for the Proposed Rates of Administration

Infusion concentrations, rates, and durations described in this protocol (see Table 4 and Table 5) are based on the experience from a shorter infusing duration of the 600 mg dose studied in ENSEMBLE Plus substudy, and from previous administration of higher doses in the RA Phase I/II studies.

ENSEMBLE Plus is the substudy for Study MA30143 designed to evaluate the safety of a shorter infusion of ocrelizumab in a subgroup of patients with early stage RRMS. In this substudy, patients who were randomized to the shorter infusion group received 600 mg ocrelizumab in 500 mL in 0.9% sodium chloride infused over 2 hours (in a blinded fashion), followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours (in order to mimic the conventional infusion duration of 3.5 hours). After first dosing, the incidence, intensity, severity, and symptoms of IRRs, as well as IRRs leading to treatment discontinuation, were comparable between the conventional and shorter infusion groups. Overall, the safety profile between the conventional and shorter infusion groups was similar.

In previous RA Phase I/II Studies WA18230 and ACT2847g, 1500 mg and 2000 mg infusions of ocrelizumab were prepared by diluting the drug product into an infusion bag containing 0.9% sodium chloride to a final drug concentration of up to 6 mg/mL, with a maximum infusion rate of 800mg/hr. A total of 85 patients were randomized to receive ocrelizumab 1000 mg: 45 to receive ocrelizumab 1500 mg and 48 to receive ocrelizumab 2000 mg. In Study WA18230, all three doses were delivered as single infusions. Most of the infusion-related adverse events were mild or moderate in severity across all treatment groups. Overall, infusions were well tolerated despite the facts that less premedications were used compared to what is required in all ongoing ocrelizumab studies and labels.

Based on the aforementioned experience, the administration procedure for this study is proposed as follows. The first dose will be split into two infusions 2 weeks apart. One infusion bag of 250 mL saline will be used for each split infusion and will contain either 300 mg, 600 mg, or 900 mg ocrelizumab, prepared in a blinded fashion. The infusion concentration and rate during these split infusions will not exceed the ones used to deliver 1000 mg in the previous MS Phase II and RA Phase I/II studies. The total infusion duration will be approximately 2h40min.

From the second dose onwards, each dose will be administered as a single infusion, for which two infusion bags (each of 500 mL saline) will be administered in a sequence. The total infusion duration will be approximately 3h40min. The first infusion bag, containing ocrelizumab 600 mg in all treatment arms, will be administered over 2hr (exactly like in ENSEMBLE Plus). The second infusion bag, containing 0 mg, 600 mg, or 1200 mg ocrelizumab, will be administered over 1h40min, without exceeding the maximum infusion rate and concentration used in the previous RA studies (i.e.,1500 and 2000 mg).

The proposed infusion rates will remain the same for all patients irrespective of the randomized treatment arm. The concentration of ocrelizumab in the infusion bags will vary depending on the randomized treatment arm. Study drug doses and treatment arms will be blinded using corresponding combinations of ocrelizumab placebo and verum vials as described in Section 4.3.1.1.

In summary, the infusion concentrations and the infusion rate (mg/hr) in this higher dose study will not exceed the highest concentrations nor the fastest infusion rate (mg/hr) used in previous studies. Based on the previous experience in MS and RA studies during which higher dose infusions were well tolerated, it is expected that the higher dose of ocrelizumab administered as proposed in this study will be well tolerated.

Refer to Section 4.3.2.1 for details on the administration rates and infusion preparation of ocrelizumab.

3.3.3 Rationale for Patient Population

This study will evaluate the efficacy of a higher dose of ocrelizumab compared with the previously studied and approved 600 mg dose on delaying disease progression in the relapsing MS patient population. Disability progression remains an important unmet medical need and a higher dose of ocrelizumab may provide a greater treatment effect on disability progression in this population.

Patient population characteristics in this study are planned to reflect the previous ocrelizumab RMS studies (WA21092 and WA21093, Opera I/II). This study will enroll patients with RMS with an EDSS score of 0–5.5 and with an age range up to ≤55 years.

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

To reduce the frequency and severity of IRRs, patients will be premedicated with 100 mg methylprednisolone IV and antihistamine given orally or by infusion, prior to administration of ocrelizumab (see Section 4.3.2.2). Administered infrequently at a low dose, methylprednisolone is not anticipated to affect the efficacy or safety outcomes of the study. An analysis of patients with MS who were treated with ocrelizumab revealed that the addition of antihistamines to the pre-treatment with methylprednisolone decreased the incidence of IRRs by two-fold (OCREVUS® U.S. Package Insert; Ocrelizumab Investigator's Brochure).

Methylprednisolone (or an alternative steroid in patients where methylprednisolone is contraindicated) and antihistamine will be administered to patients in both treatment groups.

In previous studies of ocrelizumab (see details in Appendix 11) infusions of higher doses were well tolerated with less premedication.

3.3.5 Rationale for Biomarker Assessments

MS is a heterogeneous disease. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond better to different doses of ocrelizumab. PD biomarkers will be assessed to demonstrate evidence of biologic activity of ocrelizumab in patients, compared between the dosing arms. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

B-cells are a direct PD marker for ocrelizumab, and a correlation of the extent of B-cell depletion in blood with exposure levels was observed in the ORCHESTRA Phase III trials. More sensitive tests for B-cell numbers than the TBNK test are available and will be used here to more finely map the PD response to ocrelizumab. In addition, FcγR3 genotype may act as a PD biomarker. It has been implicated in response to anti-CD20 and the ability to deplete B-cells, and linked to efficacy in RA (Cartron et al. 2002; Ruyssen-Witrand et al. 2012).

B-cell subsets have been demonstrated to be predictive of drug response (or loss of response) in rheumatoid arthritis patients, with the return of memory B-cell subsets preceding loss of efficacy in anti-CD20 treated patients (Anolik et al. 2003).

Biomarkers of neuroinflammation, NfL chain, 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 PMS 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 level, 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 (Kuhle et al. 2019; Bar-Or et al. 2019). IL–6 is an inflammatory cytokine associated with B-cell response to anti-CD20 (Barr et al. 2012) and may act as a prognostic or predictive biomarker for inflammation or progression. HLA genotype is closely linked with MS susceptibility (Hollenbach and Oksenberg 2015) and may also act as a prognostic or predictive biomarker.

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 AEs or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from 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.

3.3.6 Rationale For Measuring Impact of Ocrelizumab on Response to COVID-19 Vaccines

The results of the randomized, open-label, Phase IIIb study BN29739 (VELOCE), which assessed if ocrelizumab recipients with RMS on the approved dose of ocrelizumab raise adequate humoral responses to selected vaccines and a neoantigen, indicate that patients with RMS who are peripherally B-cell depleted after treatment with ocrelizumab can mount humoral responses, albeit attenuated, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The immune response of other components of the immune system (e.g., T-cell response), known to confer immunological protection in addition to antibodies, were not evaluated. No evidence is available regarding the effect of a higher dose of ocrelizumab on the immune response to a vaccine.

Recently, vaccines against the SARS-CoV-2 virus have received authorizations for emergency use or approvals in the US, marketing authorizations in the E.U., and/or marketing approvals from other regulatory agencies. Vaccine efficacy data and vaccine effectiveness from real world settings have shown that the available vaccines lead to a significant reduction in the number of SARS-CoV-2 infections and the number of severe cases that require hospitalization or result in fatal outcomes. Available data from the vaccine trials and real world data demonstrate that these vaccines can induce an antibody response as well as T-cell responses. Accruing evidence suggests that both antibodies and T-cell–mediated immunity have a protective role against future SARS-CoV-2 infection and severe clinical presentations (Gallais et al. 2021; Khoury et al. 2021; Lucas et al. 2021; Painter et al. 2021; Sette and Crotty 2021; Tan et al. 2021).

Emerging evidence on the COVID-19 vaccine response in persons taking the approved dose of ocrelizumab suggests that ocrelizumab attenuates the antibody response (Sormani et al. 2021), similar to what was observed in the VELOCE study testing other clinically-relevant vaccines. The antibody levels needed to confer protection are still not known. Initial results suggest that the T-cell response does not seem to be affected by ocrelizumab (Apostolidis et al. 1038; Brill et al. 2021). Additional data needs to be collected to further confirm both antibody and T-cell findings and to understand the impact on protection and disease outcomes in infected patients. Currently, it is unknown whether the immunization response will be affected differently by the higher dose of ocrelizumab compared to the standard dose. As COVID-19 vaccines induce both a robust anti-viral antibody and T-cell response, these vaccines and ongoing vaccination efforts offer an opportunity:

- To understand the possible effects of a higher dose of ocrelizumab on the immune response upon exposure to a novel antigen.
- To understand whether a higher dose of ocrelizumab may affect SARS-CoV-2 specific humoral and cellular responses.
- To help inform on effects of a higher dose of ocrelizumab on vaccine immune response beyond currently available COVID-19 vaccines.

Antibody response and cellular immune responses will be assessed before, and/or following vaccination, and/or booster doses at the regular study visit timepoints, as indicated in the SoA and Section 4.5.12.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with RMS. Approximately 786 patients will be recruited into the study

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed ICF
- Ages 18–55 years at time of screening
- Ability to comply with the study protocol
- Diagnosis of RMS (i.e., RRMS or aSPMS where patients still experience relapses) in accordance with the revised McDonald Criteria 2017 (Thompson et al. 2018)
- At least two documented clinical relapses within the last 2 years prior to screening, or one clinical relapse in the year prior to screening (with no relapse 30 days prior to screening and at baseline)
- Patients must be neurologically stable for at least 30 days prior to randomization and baseline assessments
- EDSS score, at screening and baseline, from 0 to 5.5 inclusive
- Average T25FWT score over two trials at screening and over two trials at baseline respectively, up to 150 (inclusive) seconds
- Average 9-HPT score over four trials at screening and over four trials at baseline respectively, up to 250 (inclusive) seconds
- Documented MRI of brain with abnormalities consistent with MS at screening
- Patients requiring symptomatic treatment for MS (e.g., fampridine, cannabis) and/or physiotherapy must be treated at a stable dose during the screening period prior to the initiation of study drug on Day 1 and must have a plan to remain at a stable dose for the duration of study treatment

  Patients must not initiate symptomatic treatment for MS or physiotherapy within 4 weeks of randomization.
- For females 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 ocrelizumab [Ocrevus] local label) after the final dose of ocrelizumab.

  A female is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

The following are considered adequate contraceptive methods: progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. More effective contraceptive methods (e.g., bilateral tubal ligation; male sterilization; copper intrauterine devices; combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation) may be used but are not required. 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable 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 ICF.

- For female patients without reproductive potential:

  Females may be enrolled if 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 or if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

4.1.2 Exclusion Criteria

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

- History of primary progressive MS at screening
- Any known or suspected active infection at screening or baseline (except nailbed infections), or any major episode of infection requiring hospitalization or treatment with IV antimicrobials within 8 weeks prior to and during screening or treatment with oral antimicrobials within 2 weeks prior to and during screening
- History of confirmed or suspected progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening

  Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary.

- Immunocompromised state, defined as one or more of the following:

  CD4 count $<$ 250/μL or absolute neutrophil count $<$ 1.5×10^3/μL or serum IgG $<$ 4.6 g/L

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

  Influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Inability to complete a 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 gadolinium administration
- Contraindications to mandatory pre-medications (i.e., corticosteroids and antihistamines) for IRRs, including uncontrolled psychosis for corticosteroids or 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 ischemic cerebrovascular disorders (e.g., stroke) or ischemia of the spinal cord

  History or known presence of clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression), or clinically significant CNS or spinal cord tumor (e.g., meningioma, glioma)

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

  History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus type 1, herpes zoster myelopathy)

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

  Neuromyelitis optica spectrum disorders

  History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease, or sarcoidosis)
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- 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
- History of or currently active primary or secondary (non–drug-related) immunodeficiency
- Pregnant or breastfeeding or intending to become pregnant during the study or 6 or 12 months (as applicable from the local label for ocrelizumab) after final dose of the study drug

Females of childbearing potential must have a negative serum and urine pregnancy test result prior to initiation of study drug (negative serum β-hCG measured at screening and negative urine β-hCG at baseline)

- Lack of peripheral venous access
- History of alcohol or other drug abuse within 12 months prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or five 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 use of anti-CD20s (including ocrelizumab), unless the last infusion was more than 2 years before screening, B-cell count is normal, and the stop of the treatment was not motivated by safety reasons or lack of efficacy
- Any previous treatment with mitoxantrone, cladribine, atacicept, alemtuzumab, and daclizumab
- Previous treatment with fingolimod, siponimod, or ozanimod within 6 weeks of baseline
- Previous treatment with natalizumab within 4.5 months of baseline
- Previous treatment with interferons beta (1a or 1b), or glatiramer acetate within 2 weeks of baseline
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label (washout to be completed prior to baseline). If the washout requirements are not described in the applicable local label, then the wash out period must be five times the half-life of the medication. The PD effects of the previous medication must also be considered when determining the required time for washout.

  Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.
- 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

  For a patient to be eligible, systemic corticosteroids should also not have been administered between screening and baseline.
- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):

  Positive hepatitis B surface antigen

  Positive hepatitis B core antibody (total HBcAb) and detectable hepatitis B virus DNA

- Sensitivity or intolerance to any ingredient (including excipients) of ocrelizumab
- Any additional exclusionary criterion as per ocrelizumab (Ocrevus) local label, if more stringent than the above

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 as soon as possible, or within maximum 4 weeks within the allowed screening period. 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 criteria may participate in the OLE phase:

- Completed the DBT phase of the trial and who, in the opinion of the investigator, may benefit from treatment with a higher dose of ocrelizumab

  Patients who withdrew from study treatment, including patients who received another disease-modifying therapy will not be allowed to enter the OLE phase.
- Able and willing to provide written informed consent to participate in the OLE phase and to comply with the study protocol
- Meet the re-treatment criteria for ocrelizumab (see Section 4.3.2.3)
- For females 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 ocrelizumab [Ocrevus] local label) after the final dose of ocrelizumab

  A female is considered to be of childbearing potential if she is postmenarchal, has not reached a post-menopausal 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

The following are considered adequate contraceptive methods progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. More effective contraceptive methods (e.g., bilateral tubal ligation; male sterilization; copper intrauterine devices; combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation) may be used but are not required. 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable 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 ICF

- For female patients without reproductive potential:

  Females may be enrolled if 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 or if surgically sterile (i.e., hysterectomy, complete bilateral oophorectomy).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening and baseline procedures and assessments have been completed, and eligibility has been established for a patient, the patient will be assigned an identification number and treatment assignment by an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: higher dose or approved dose of ocrelizumab. Randomization will occur in a 2:1 ratio (higher dose to approved dose, respectively) through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- Weight at baseline ($<$ 75 kg vs. $\geq$ 75 kg)
- Region (United States vs. ROW)
- EDSS ($<$ 4 vs. $\geq$ 4)
- Age at screening ($\leq$ 45 years vs. $>$ 45 years)

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. 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 will be documented in a separate study

document and may include, but may not be limited to, the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members. The handling of the investigational medicinal product (IMP) by the pharmacist as well as the process to maintain the blind is described in the pharmacy manual. 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; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the treatment assignment for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to unblinding of treatment assignment, the investigator will be able to break the treatment code by contacting the IxRS.

Any unblinding at the investigating site will be documented in the study report with the date, reason for identifying the assigned treatment/drug dose and name of the persons who requested the 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.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the DBT phase as a result of AEs 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

(where required) in administering and scoring the EDSS, 9-HPT, Functional System Scores (FSS), and SDMT. The Examining Investigator (or their designee) will assess the EDSS, T25FWT, 9-HPT, and SDMT. During the DBT phase, the Examining Investigator and their qualified designees (if applicable) will not be involved with any aspect of the medical management of the patient and will not be allowed access to patient data. They will also not discuss any treatment aspects (i.e., AEs) with the patient.

The Treating Investigator and the Examining Investigator will not be allowed to switch roles. During the DBT, an investigator/site staff at a single site must not be a Treating Investigator for some patients and an Examining Investigator for others.

The Treating Investigator will confirm the screening and baseline eligibility criteria for EDSS, 9-HPT, and T25FWT by accessing the relevant reports.

- Patient education: During the DBT phase, prior to being examined by the Examining Investigator, patients should be instructed not to discuss with the Examining Investigator what (if any) AEs they may be experiencing.
- Blinded, central MRI assessments: A blinded, central MRI reader will assess all MRI scans performed during the study. During the DBT phase, only the local radiologist/technician at the investigational site who is assigned to this study may have access to the MRI scans. Of note, baseline MRI scan will be used for the assessment of patient eligibility, and therefore it will not be blinded. 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 (refer also to Section 4.5.7).
- 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, ANC, CD4) and Ig levels will be blinded in all patients until the start of OLE, which will occur after the primary analysis is complete. 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 (via reflex messages). Refer to the laboratory manual for additional information.
- Treatment allocation will remain blinded at least until the primary analysis *is performed and the decision to start the OLE is communicated by the Sponsor*.

  Of note, the blinding procedures are not necessary during the OLE phase. It is, however, recommended that the same Examining Investigator continues to perform the assessments throughout the OLE phase as in the DBT phase.

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. Premedications, such as methylprednisolone (or equivalent) and antihistamines (such as diphenhydramine or equivalent) are considered *auxiliary medicinal products (AxMPs)*/non-investigational medicinal products (NIMPs). *Appendix 17 identifies all IMPs and AxMPs/NIMPs for this study.*

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Ocrelizumab and Placebo Vials

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. The solution should not be used if discolored or if the solution contains discrete foreign particulate matter. Ocrelizumab solutions for IV administration will be prepared by dilution of ocrelizumab in infusion bags containing 0.9% sodium chloride, as specified in Table 2, Table 3, Table 4, and Table 5. 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).

Ocrelizumab matching placebo vials will be used in the study to enable blinding of the study drug doses across the study arms. Placebo vials will be supplied by the Sponsor. These placebo vials will have the same composition and configuration as the drug product but will not contain ocrelizumab.

Each study medication kit will contain 1 single-use vial of either 300 mg ocrelizumab or ocrelizumab placebo. Medication kits will be dispensed via IxRS system in a blinded fashion allowing for administration of the various study drug dose configurations.

For the DBT, in Dose 1 consisting of two infusions 14 days apart, the following blinded study medication kits will be dispensed according to the assigned treatment arm:

- Infusion 300 mg: one ocrelizumab verum vial and two ocrelizumab placebo vials
- Infusion 600 mg: two ocrelizumab verum vials and one ocrelizumab placebo vial
- Infusion 900 mg: three ocrelizumab verum vials

For each of the subsequent study doses, the following blinded study medication kits will be dispensed for the first and second infusion bag according to the assigned treatment arm:

- Infusion 600 mg: two ocrelizumab verum vials for the first infusion bag, and four ocrelizumab placebo vials for the second infusion bag

- Infusion 1200 mg: two ocrelizumab verum vials for the first infusion bag, and two ocrelizumab verum vials plus two ocrelizumab placebo vials for the second infusion bag
- Infusion 1800 mg: two ocrelizumab verum vials for the first infusion bag, and four ocrelizumab verum vials for the second infusion bag

In the OLE phase, ocrelizumab vials will not be blinded.

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab Investigator's Brochure, local prescribing information, and drug preparation guidelines (pharmacy manual). Refer also to Section 4.3.2.1 for details on study treatment dosage and administration of infusions.

4.3.1.2 Non-Investigational/*Auxiliary* Medicinal Products

In this study, NIMPs/*AxMPs* will include premedication to the ocrelizumab infusion. The following premedication will be used:

- Mandatory methylprednisolone (or equivalent)
- Mandatory antihistaminic drug (e.g., diphenhydramine or equivalent)
- 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 4.3.2.1. Details on treatment administration (e.g., infusion administration and timing) should be noted on the Study Drug Administration eCRF. Any infusion modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment modification, interruption, or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration, as well as the process to maintain the blind.

4.3.2.1 Ocrelizumab Approved Dose and Higher Dose

Both the approved 600 mg dose and the higher dose (1200 mg [patient's body weight < 75 kg at baseline] or 1800 mg [patient's body weight ≥ 75 kg at baseline]) of ocrelizumab will be administered in a blinded fashion every 24 weeks. The first dose of ocrelizumab will be administered as two IV infusions (either 300 mg or 600/900 mg) given 14 days apart (refer to Table 1 in Section 3.1). A minimum interval of 20 weeks must be maintained between the second infusion of the first dose and the infusion of the second dose of ocrelizumab. For the subsequent doses, ocrelizumab will be

administered as a single 600 mg (approved dose) or 1200/1800 mg (higher dose) IV infusion every 24 weeks. A minimum interval of 22 weeks must be maintained between each subsequent dose of ocrelizumab administered as single infusions. *Minimum dosing intervals are to be used in exceptional circumstances only and visits should be scheduled according to the SoA outlined in Appendix 1.*

The 600 mg dosing regimen applied in this study as control is consistent with the dosing regimen used in the ocrelizumab Phase III/IV studies, as well as with the Summary of Product Characteristics and the U.S. Prescribing Information.

Ocrelizumab infusions should be initiated and supervised by an experienced health care professional with access to appropriate medical support to manage severe reactions such as serious IRRs. It is anticipated that the patient may need to stay at the hospital or clinical site for a full day at an infusion visit.

*During the DBT, e*ach ocrelizumab split dose (i.e., the first dose, either 300 mg or 600/900 mg) infusion should be administered as a slow IV infusion over approximately 2 hours and 40 minutes. Each subsequent ocrelizumab full dose (600 mg or 1200/1800 mg) infusion should be administered as a slow IV infusion over approximately 3 hours and 40 minutes. Refer to Table 2, Table 3, Table 4, and Table 5 for details on dosing preparations and administration *during the DBT*.

Table 2 Rates of Infusion for Initial Dose (600 mg)

Control Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
Initial dose (600 mg), divided into two infusions	Infusion 1	Only one infusion bag of 250 mL 0.9% sodium chloride	Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
			0-30	30	18	18
	Infusion 2 (2 weeks later)	Take out 30 mL saline before adding 3 blinded vials as assigned by IxRS	31-60	60	36	54
			61-90	90	54	108
			91-120	120	72	180
			121-150	150	90	270
			151-159	180	30	300
			Total infusion time: approx. 2h39min			

approx.=approximately; IV=intravenous; IxRS=interactive voice or web-based response system.

Table 3 Rates of Infusion for Initial Dose (1200 mg and 1800 mg)

Higher Dose Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
Initial dose (1200 mg Higher Dose Group), divided into two infusions	Infusion 1	Only one infusion bag of 250 mL 0.9% sodium chloride	Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
	Infusion 2 (2 weeks later)	Take out 30 mL saline before adding 3 blinded vials as assigned by IxRS	0-30	30	36	36
			31-60	60	72	108
			61-90	90	108	216
			91-120	120	144	360
			121-150	150	180	540
			151-159	180	60	600
			Total infusion time: approx. 2h39min			
Initial dose 1800 mg Higher Dose Group, divided into two infusions	Infusion 1	Only one infusion bag of 250 mL 0.9% sodium chloride	Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
	Infusion 2 (2 weeks later)	Take out 30 mL saline before adding 3 blinded vials as assigned by IxRS	0-30	30	54	54
			31-60	60	108	162
			61-90	90	162	324
			91-120	120	216	540
			121-150	150	270	810
			151-159	180	90	900
			Total infusion time: approx. 2h39min			

approx.=approximately; IV=intravenous; IxRS=interactive voice or web-based response system.

Table 4 Rates of Infusion for Subsequent Doses (600 mg)

Control Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
			Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
Subsequent doses (600 mg Control Group)	Infusion 3 and following	First infusion bag: 500 mL 0.9% sodium chloride Add 2 blinded vials as assigned by IxRS. Do not remove any saline. Total volume: 520 mL*, ocrelizumab concentration: 1.2 mg/mL Second infusion bag: 500 mL 0.9% sodium chloride Take out 40 mL saline before adding 4 blinded vials as assigned by IxRS Total volume: 500 mL, OCR concentration: 0 mg/mL	First infusion bag			
			0-15	100	30	30
			16-30	200	60	90
			31-60	250	150	240
			61-90	300	180	420
			91-120	300	180	600
			Second infusion bag			
			121-150	300	0	600
			151-180	300	0	600
			181-210	300	0	600
			211-220	300	0	600
			Total infusion time: approx. 3h40min			

approx.=approximately; IV=intravenous; IxRS=interactive voice or web-based response system; OCR=ocrelizumab.

* *The full volume prepared should be administered, which may extend the infusion time beyond 120 minutes.*

Table 5 Rates of Infusion for Subsequent Doses (1200 mg and 1800 mg)

Higher Dose Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
			Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
Subsequent doses (1200 mg) Higher Dose Group	Infusion 3 and following	First infusion bag: 500 mL 0.9% sodium chloride Add 2 blinded vials as assigned by IxRS. Do not remove any saline. Total volume: 520 mL*, ocrelizumab concentration: 1.2 mg/mL Second infusion bag: 500 mL 0.9% sodium chloride Take out 40 mL saline before adding 4 blinded vials as assigned by IxRS Total volume: 500 mL, OCR concentration: 1.2 mg/mL	First infusion bag			
			0-15	100	30	30
			16-30	200	60	90
			31-60	250	150	240
			61-90	300	180	420
			91-120	300	180	600
			Second infusion bag			
			121-150	300	180	780
			151-180	300	180	960
			181-210	300	180	1140
			211-220	300	60	1200
			Total infusion time: approx. 3h40min			

approx.=approximately; IRR=infusion-related reaction; IV=intravenous; IxRS=interactive voice or web-based response system; OCR=ocrelizumab.

* *The full volume prepared should be administered, which may extend the infusion time beyond 120 minutes.*

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for IRRs. Prior to the infusions, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Table 5 Rates of Infusion for Subsequent Doses (1200 mg and 1800 mg) (cont.)

Higher Dose Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
			Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
Subsequent doses (1800 mg) Higher Dose Group	Infusion 3 and following	First infusion bag: 500 mL 0.9% sodium chloride Add 2 blinded vials as assigned by IxRS. Do not remove any saline. Total volume: 520 mL*, ocrelizumab concentration: 1.2 mg/mL	First infusion bag			
			0-15	100	30	30
			16-30	200	60	90
			31-60	250	150	240
			61-90	300	180	420
			91-120	300	180	600
		Second infusion bag: 500 mL 0.9% sodium chloride Take out 40 mL saline before adding 4 blinded vials as assigned by IxRS Total volume: 500 mL, OCR concentration: 2.4 mg/mL	Second infusion bag			
			121-150	300	360	960
			151-180	300	360	1320
			181-210	300	360	*1680*
			211-220	300	120	1800
			Total infusion time: approx. 3h40min			

approx.=approximately; IRR=infusion-related reaction; IV=intravenous; IxRS=interactive voice or web-based response system; OCR=ocrelizumab.

** The full volume prepared should be administered, which may extend the infusion time beyond 120 minutes.*

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for IRRs. Prior to the infusions, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Refer to Table 6 for details on dosing preparations and administration during the OLE phase.

Table 6 Rates of Infusion for OLE Doses (1200 mg and 1800 mg)

Higher Dose Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
			Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
1200 mg	OLE	**First infusion bag:** 500 mL 0.9% sodium chloride Add 2 ocrelizumab 300 mg IV vials as assigned by IxRS. Do not remove any saline. Total volume: 520 mL, ocrelizumab nominal concentration: 1.2 mg/mL **Second infusion bag:** 250 mL 0.9% sodium chloride Take out 20 mL saline before adding 2 ocrelizumab 300 mg IV vials as assigned by IxRS Total volume: 250 mL, OCR nominal concentration: 2.4 mg/mL	**First infusion bag**			
			0-15	100	30	30
			16-30	200	60	90
			31-60	250	150	240
			61-90	300	180	420
			91-120	300	180	600
			Second infusion bag			
			121-150	300	360	960
			151-170	300	240	1200
			Total infusion time: approx. 2h50min			

approx. =approximately; IRR =infusion-related reaction; IV =intravenous; IxRS =interactive voice or web-based response system; OCR =ocrelizumab.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for IRRs. Prior to the infusions, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Table 6 Rates of Infusion for OLE Doses (1200 mg and 1800 mg)(cont.)

Higher Dose Group	Preparation of the Infusion for IV Administration		Infusion Rates, Time, and Dose per Intervals			
			Time in minutes	Infusion rate (mL/hr)	Max dose per interval (mg)	Cumulative dose (mg)
			First infusion bag			
			0-15	100	30	30
			16-30	200	60	90
			31-60	250	150	240
			61-90	300	180	420
			91-120	300	180	600
			Second infusion bag			
			121-150	300	360	960
			151-180	300	360	1320
			181-210	300	360	1680
			211-220	300	120	1800
1800 mg	OLE	**First infusion bag:** 500 mL 0.9% sodium chloride Add 2 ocrelizumab 300 mg IV vials as assigned by IxRS. Do not remove any saline. Total volume: 520 mL, ocrelizumab nominal concentration: 1.2 mg/mL **Second infusion bag:** 500 mL 0.9% sodium chloride Take out 40 mL saline before adding 4 ocrelizumab 300 mg IV vials as assigned by IxRS Total volume: 500 mL, OCR nominal concentration: 2.4 mg/mL	Total infusion time: approx. 3h40min			

approx. =approximately; IRR =infusion-related reaction; IV =intravenous; IxRS =interactive voice or web-based response system; OCR =ocrelizumab.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for IRRs. Prior to the infusions, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

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 AEs 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 IRRs. An analysis of patients with MS treated with ocrelizumab revealed that the addition of antihistamines pre-treatment with methylprednisolone decreased the incidence of IRRs by two-fold (OCREVUS® U.S. Package Insert; Ocrelizumab Investigator's Brochure).

To reduce potential IRRs, all patients must receive mandatory prophylactic treatment with 100 mg of methylprednisolone administered by IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion. In the rare case when the use of methylprednisolone is contraindicated for the patient, an equivalent dose of an alternative IV steroid should be used.

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

An analgesic/antipyretic (i.e., acetaminophen/paracetamol 1 g) can also be considered.

Hypotension (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 Retreatment 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

Of note: the above laboratory parameters (ANC, CD4, and IgG) will be blinded in all patients throughout the DBT phase. Investigators will be notified of their patient's abnormal laboratory test results via blinded reflex messages from the central

laboratory. Refer also to Section 4.2.2 and to the laboratory manual for details on blinding of laboratory parameters.

- Negative urine pregnancy test before infusion

  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. Following a discussion with the investigator, pregnant and breastfeeding patients can continue to follow the schedule of activities for the study; however, no infusions will occur. Note that certain tests and assessments may be contraindicated in pregnancy and should therefore be skipped at the discretion of the Treating Investigator. If there is a concern with the ability of a pregnant or breastfeeding patient to perform the scheduled assessments, the investigator should 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 Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., 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. Immediately upon receipt, 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 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 ocrelizumab Investigator's Brochure 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 an open-label extension of this study, as described in Section 3.1. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and 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 should be reported to the investigator and recorded in their respective eCRFs.

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 treatment discontinuation (see Section 4.7.1).

4.4.3 Prohibited Therapy and Alternative Treatment Post-Ocrelizumab

The following therapies for MS are not permitted while under study treatment: B-cell targeted therapies (e.g., rituximab, atacicept, belimumab, ofatumumab, or others), 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. If patient prematurely discontinues the randomized treatment and starts an approved MS DMT medication, they will continue to be followed up in DBT phase until primary analysis (please refer to Section 3.1.1.2). 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. Known dates of immunizations will be recorded on specific eCRF pages (i.e., Vaccination History; refer also to Section 4.5.2). Any required immunizations should be completed at least 6 weeks prior to first administration of ocrelizumab.

Immunization with any live or live-attenuated vaccine (e.g., 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. 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 schedule of activities to be performed during the study is provided in Appendix 1, Appendix 2, and Appendix 3.

All activities should be performed and documented for each patient. Note that baseline assessments related with the eligibility (e.g., EDSS, 9-HPT, and T25FWT), should be conducted prior to the patient being randomized into the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

The screening data for all patients (including those who have been screen failed) will be captured by the sites in the eCRF.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including, but not limited to, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, will be recorded at screening and re-confirmed at baseline.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, 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. Vaccinations received within 10 years prior to screening and throughout the study will be collected. 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 DMTs taken for the treatment of MS at any time 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 in the eCRF.

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 and baseline and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. Measurement of weight at screening, baseline, and throughout the study treatment will also be performed. Measurement of height will be taken at screening.

Limited, symptom-directed physical examinations should be performed at specified post-baseline 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 AE eCRF.

4.5.4 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. A neurologic examination should include an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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 9 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 9). The Medical Monitor should be immediately contacted by telephone as well as by email.

A patient with confirmed PML should be discontinued 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).

4.5.5 Assessment of Disability and New or Worsening Neurological Events

4.5.5.1 Assessment of Disability

In this study, MS disability will be measured by the following Clinician Reported Outcome Assessments and performance outcomes: EDSS, 9-HPT, and T25FWT. Additionally, SDMT will be performed (see Section 4.5.9.2 for test descriptions). Assessments will be administered by the Examining Investigator (see role description in Section 4.2) at the timepoints indicated in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3). All these assessments will be captured electronically.

Patients will be evaluated for any new or worsening neurological event (including relapse) by the Treating Investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm an event occurring between the visits.

Should a new or worsening neurological event occur, the patient should be referred by the Treating Investigator to the Examining Investigator or their qualified designee (as applicable) who will independently assess the EDSS, 9-HPT, and T25FWT to establish the current neurological status of the patient. Additionally, SDMT will be performed. The above assessments should be performed within 7 days from the onset of a new or worsening neurological event.

4.5.5.2 Assessment of Relapse

In case of a clinical relapses, the EDSS score will allow confirmation as to whether or not the clinical relapse(s) meet the criteria for protocol-defined relapse(s). All new or worsening neurological events compatible with MS representing a clinical relapse are to be reported on a dedicated eCRF page.

EDSS, 9-HPT, T25FW, and SDMT should be performed within 7 days from the onset of the relapse.

For this study, a protocol-defined 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
- Two points on one of the selected FSS as listed below
- One 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.

It should be noted that all patients with new neurological symptoms defined at a visit 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.

All clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) will be recorded in the eCRF. Determination of whether a clinical relapse fulfills the definition of a protocol-defined relapse will be performed by the Sponsor.

4.5.6 Vital Signs

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

*During the DBT phase, o*n the infusion days, blood pressure, pulse rate, and temperature should be taken within 45 minutes prior to the premedication (methylprednisolone or equivalent and antihistamines). In addition, vital signs should be obtained immediately prior to the ocrelizumab infusion, then every 15 minutes (±5 minutes) for the first hour, followed by every 30 minutes (±10 minutes) for the remaining of the infusion, at the end of the infusion, and then 30 minutes (±10 minutes) and 1 hour (±10 minutes) after the end of the infusion. On the non–infusion days, the vital signs may be taken at any time during the visit.

During the OLE phase, on infusion days, blood pressure, pulse rate, and temperature should be taken within 45 minutes prior to the premedication (methylprednisolone or equivalent and antihistamines), immediately prior to the ocrelizumab infusion and 1 hour (±10 minutes) after the end of the infusion. In the event of an IRR, in addition to the timepoints above, vital signs should also be recorded every 15 minutes (±5 minutes) in the first hour after the onset of the IRR, followed by every 30 minutes (±10 minutes) until 1 hour (±10 minutes) after the end of the infusion.

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 AE or IRR/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.

4.5.7 MRI Sequences

MRI will be used to monitor CNS lesions in patients with MS and potentially other pathophysiology, such as inflammation and neurodegeneration. MRI scans of the brain,

and also of the upper part of the spine if technically possible will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, and Appendix 3.

The MRI sequences will be analyzed by a central reading facility ensuring the integrity and quality of the acquired data.

Qualifying MRI scans will be performed on healthy volunteers having provided informed consent at each MRI center as part of the scanner certification process with the MRI service provider, if not already available.

During the screening phase, one MRI scan will be performed, and it will serve as a baseline scan. Note that this baseline scan should be obtained 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.

Post-baseline, MRI scans will be obtained in all patients as per Schedule of Activities (SoA, see Appendix 1, Appendix 2, and Appendix 3). In addition, MRI scans will be obtained at *the* treatment discontinuation visit if one was not performed during the prior 4 weeks. 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, and Appendix 3). During the OLE, MRI scans will be performed every 48 weeks (according to the yearly schedule as carried over from the double-blind treatment phase).

If patients receive corticosteroids for an MS relapse, every effort should be made to obtain scheduled MRI scan prior to the first corticosteroid dose. 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. For details of the MRI sequences, scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI scanner, and the procedures for the blinded analysis of the scans at the central reading center, refer to the MRI Acquisition Procedures Manuals.

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. Exploratory sequences will be read by an external partner to support future research purposes.

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 DBT phase, only the local radiologist/technician at the investigational site that 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 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.

Given the complexity and exploratory nature of exploratory MRI 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.

4.5.8 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, white blood cells (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
- Quantitative Ig: Ig levels (IgG, IgM, and IgA)
- Anti-Drug Antibodies (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 1and Appendix 2). 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, and Appendix 3. 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.

- FSH level testing: only applicable to female patients to confirm the post-menopausal status at screening. Additionally, FSH level should be tested prior to OLE entry (OLE screening), if applicable.
- Viral serology and detection: All patients must have negative hepatitis B surface antigen (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 *at the clinic visits* (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 *for confirmation*. 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; they will be however further followed up for safety and efficacy (see Section 4.7.1).

  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 discontinued from the treatment (see Section 4.7.1). 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 samples for the following tests should be drawn prior to infusion according to the SoA timepoint and will be sent to the central laboratory and/or to the Sponsor or designated processing site, and may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (contract research organization and/or academic research laboratory affiliated with the study).
- Flow cytometry: Analysis will include, but is not limited to, the determination of the B-cell number (CD19+), high-sensitivity assay B-cell counts, 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+).

The following samples will be sent to one or several designated central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK analysis
- A plasma and a serum sample will be collected and analysis may include, but will not be limited to, NfL

- A blood sample will be collected for the extraction of DNA and analysis may include but will not be limited to the FcγR3 genotype or HLA genotype. NGS methods may include WGS or WES of blood samples, or PCR of specific genotypes or other methods of HLA genotyping, but only at participating sites (see Section 4.5.10). Candidates 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).

All laboratory samples collected during the study will be shipped to a central laboratory, or one or more laboratories designated by the Sponsor for analysis, with the exception of urine dipsticks/urine probes, which will be analyzed locally unless otherwise indicated. For additional details on testing, refer to Laboratory Manual.

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

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

Unless the patient gives specific consent for their leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report (CSR) has been completed, with the following exception:

- All samples collected for biomarker research will be destroyed no later than 5 years after the final CSR has been completed.

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.

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

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

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

4.5.9 Clinical Outcome Assessments

Patient reported outcomes (PRO), clinician reported outcomes (ClinRO), and performance outcomes (PerfO) measures will be completed to assess the treatment benefit of a higher dose of ocrelizumab relative to the approved dose.

All measures will be completed in their entirety at specified timepoints throughout 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.

PRO data will be collected using the following measures, in the following order: MSIS-29 v2, PGI-S, PGI-C, Neuro-QoL Upper Extremity Function, PGI-C-UL, MSWS-12, MFIS, and EQ-5D-5L.

ClinRO data will be collected through use of Neurostatus e-EDSS.

PerfO data will be collected through use of the following instruments: T25FWT, 9-HPT, and SDMT.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints throughout the study (see schedule of activities in Appendix 1, Appendix 2, and Appendix 3.

PRO instruments, translated into the local language as appropriate, will be completed using an electronic device provided by the Sponsor. The device will be pre-programmed to ensure the appropriate PROs, EDSS and PerfOs are administered in a standardized order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. For all Clinical Outcome Assessments (COAs), 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. A web-based back-up option will be available if required. For consistency, formatting of each PRO will remain the same as observed on the tablet.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be between 10–20 minutes at each specified visit.

- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.9.2 Clinician Reported Outcome Assessments and Performance Outcomes

ClinRO and PerfO instruments will be administered at clinic by a physician or appropriate delegate and completed using an electronic device provided by the Sponsor, at specified timepoints throughout the study (see Appendix 1, Appendix 2, and Appendix 3). Clinicians must complete the official version of each ClinRO and PerfO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol. The data will be transmitted to a centralized database maintained by the electronic device vendor. All instruments apart from EDSS will have a web-based back-up option if required, from study start. EDSS will have a paper back-up option from study start, which is envisaged to be replaced by a web-based option. Please note that once the web-based option is available, the paper option should no longer be used by the study sites.

Expanded Disability Status Scale (EDSS)

The EDSS is the most commonly used ClinRO measure for quantifying changes in the disability level of patients with MS over time. 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 EDSS is based on a standard neurological examination, incorporating functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral [or mental]) that are rated and then scored as a FSS, and ambulation, which is scored as ambulation score. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and an ambulation score that is rated from 0 to 16. These ratings are then used in conjunction with observations, as well as information, concerning ambulation and use of assistive devices to determine the total EDSS score. All FSS, ambulation score, and total EDSS scores will be captured electronically.

EDSS 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, and Appendix 3).

In this study, Neurostatus-eEDSS definitions and calculating algorithms will be used. (D'Souza et al. 2017). Note that fatigue, although it is a required subscore, will not contribute to the scoring algorithm. Sexual dysfunction does not need to be scored.

9-Hole Peg Test (9-HPT)

The 9-HPT is a performance measure used to assess upper extremity (arm and hand) function (Goodkin et al. 1988; Fischer et al. 1999b). The test 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). A 20% change from baseline is typically considered clinically meaningful (Feys et. al. 2017).

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, and Appendix 3). The 9-HPT will be administered as described in the MSFC Administration and Scoring Manual (Fischer et al. 2001).

Timed 25-Foot Walk Test (T25FWT)

The T25FWT test is a performance measure used to assess walking speed based on a timed 25-foot walk. The patient is directed to start at one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly and safely as possible. The Examining Investigator will time the patient from the start of the walk to the end of the 25 feet. The task is immediately administered again by having the patient walk back the same distance. The score for the T25FWT is the average of the two completed trials. Patients may use assistive devices (e.g., cane, crutch, or rollator) when performing the task. The Examining Investigator should assess which assistive device is necessary and try to use the same assistive device at each study visit, whenever possible. Non–wheeled walkers should not be used. Circumstances that may affect the patient's performance, or if the patient cannot complete the T25FWT twice, should be reported. The T25FWT will be administered as described in the MSFC Administration and Scoring Manual (Fischer et al. 2001). A 20% change from baseline of the averaged T25FWT is typically considered clinically meaningful (Hobart et. al. 2013; EMA 2019).

The T25FWT 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, and Appendix 3).

Symbol Digit Modalities Test (SDMT)

The SDMT is a performance measure that 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 (Smith 1982). 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. A four-point change from baseline is typically considered clinically meaningful (Benedict et. al. 2017).

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, and Appendix 3).

4.5.9.3 Patient Reported Outcome Assessment Instruments

EuroQol 5-Dimension Questionnaire, 5-Level (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; Appendix 12). 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 (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete and will be administered at baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter. This measure will be used for informing pharmacoeconomic evaluations resulting from this study.

Multiple Sclerosis Impact Scale-29 (MSIS-29)

The MSIS-29 (Version 2) 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 4). 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. This will be administered at screening, baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter.

Modified Fatigue Impact Scale (MFIS)

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; Appendix 5). 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. This will be administered at screening, baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter.

Quality of Life in Neurological Disorders-Upper Extremity Function (Neuro-QoL Upper Extremity Function)

The Neuro-QoL Upper Extremity Function (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; Appendix 6). 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 20 and divided by (20 minus the number of any unanswered items). Scores range from 20–100, where a higher score indicates better upper limb function. In accordance with the 2015 manual, scores can be calculated as long as at least 50% of the items have been answered. This will be administered at screening, baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter.

Multiple Sclerosis Walking Scale-12 Item (MSWS-12)

The MSWS-12 is a 12-item self-report measure of the impact of MS on the individual's ability to walk during the past 2 weeks (see Appendix 7; Hobart et al. 2003). Each item is scored on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely). Scores are summed and converted to a 0–100 scale with higher scores indicating greater impact of MS on walking ability. An 8-point change is considered clinically meaningful (Meht et al. 2015). This will be administered at screening, baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter.

Patient Global Impression of Severity (PGI-S)

The PGI-S is a single-item assessment of a patient's impression of the severity of his or her MS symptoms over the past 7 days (see Appendix 13). Patients are asked to respond on a 5-point Likert scale from "none" (1) to "very severe" (5). The PGI-S is used with the PGI-C as an anchor for calculating a clinically meaningful change in the MSIS-29. This will be administered at screening, baseline and during clinic visits, prior to treatment administration, every 24 weeks thereafter.

Patient Global Impression of Change (PGI-C)

The PGI-C is a single item completed by the patient to assess changes in fatigue over the last 6 months (see Appendix 14). Patients will be asked to respond on a 7-point Likert scale from "very much better" (1) to "very much worse" (7). The PGI-C is used with the PGI-S as an anchor for calculating a clinically meaningful change in the MSIS-29. This will be administered during clinic visits, prior to treatment administration, every 24 weeks following baseline.

Patient Global Impression of Change for Upper Limb Function (PGI-C-UL)

The PGI-C-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 15). 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 PGI-C-UL is used as an

anchor to determine what is a clinically meaningful change in the Neuro-QoL Upper Extremity Function. This will be administered during clinic visits, prior to treatment administration, every 24 weeks following baseline.

4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES 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 or WES, this section of the protocol (Section 4.5.10 will not be applicable at that site).

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

Blood samples collected for WGS or WES 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 ICF and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.8 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 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 biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The

collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/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 4.5.11) will not be applicable at that site.

4.5.11.3 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 diseases, or drug safety:

- Optional RBR blood sample for DNA
- Optional RBR blood sample for plasma
- Optional RBR blood sample for RNA (Paxgene)
- Leftover blood, serum, plasma, peripheral blood mononuclear cell (PBMC), including remaining blood or CSF samples collected in the substudy, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and

safety or predicting which patients are more likely to respond to a drug or develop adverse events.

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

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

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

4.5.11.4 Confidentiality

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

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

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each 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 samples. Patients who decline to participate will not provide a separate signature.

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

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

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the 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 RBR 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 this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

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

4.5.12 Analysis of Immune Responses Following COVID-19 Vaccination (Optional Procedure)

Note: this section only applies to patients who consented to the optional procedure and started the collection of samples prior to Aug 1st, 2023. No new patients should be consented after this date and no samples collected in new patients.

The ICF will contain a separate section that addresses this optional procedure. A separate signature will be required to document the patient's agreement to undergo this optional procedure.

Collection of samples for COVID-19 vaccine immunological assessments (please see Figure 2 for details):

1. Patients who receive the COVID-19 vaccine and who consent to provide the blood samples before the vaccination has occurred:

   The analyses of anti–SARS-CoV-2 antibody titers and T-cell responses will be performed at a maximum of four timepoints:

   1. At the study visit when the patient signs the ICF for this procedure, prior to the administration of the vaccine
   2. At the next study visit(s), up to a maximum of three visits following completion of vaccination: study visit following completion of vaccination, and approximately 6 months and 12 months after completion of vaccination.

1. Patients who receive the COVID-19 vaccine and who consent to provide blood samples within approximately 1 year (48 weeks) after the complete vaccination has occurred (after one dose for a single-dose vaccine or after the second dose for a two dose vaccine):

   The analyses of anti–SARS-CoV-2 antibody titers and T-cell responses will be performed up to a maximum of three timepoints depending on when the patient signed the optional procedure ICF and when the vaccination was completed:

   1. At the study visit following completion of vaccination, and approximately 6 months and 12 months after completion of vaccination

3. Patients who receive a COVID-19 vaccine booster dose:

   The analyses of anti–SARS-CoV-2 antibody titers and T-cell responses will be performed up to a maximum of two timepoints depending on when the patient signed the optional ICF and when the booster dose was administered:

1. At the study visit closest to the booster dose and visit closest to 6 months after the booster dose. The booster dose will override the schedule of any previous post-vaccination sample collection. Samples will not be collected for additional vaccine booster doses.

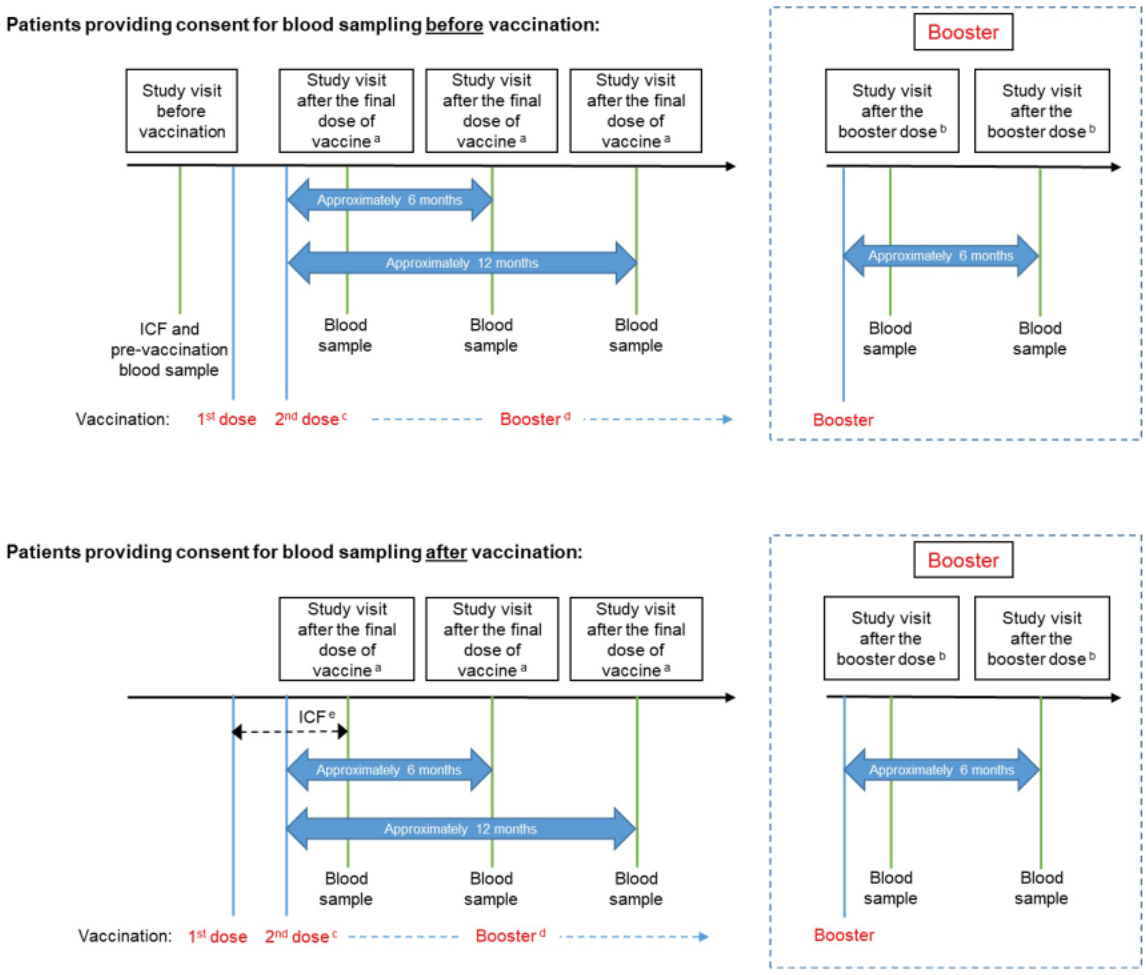
Samples will be collected at the regular study visits described in the SoA. Samples to be collected will include the following:

1. A serum sample to evaluate the humoral immunity, including antibody titers.
2. A whole blood sample, processed locally and then sent to the central lab for analysis of the T-cell response.

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

Figure 2 Overview of Sample Collection for COVID-19 Vaccine Immunological Assessments for Optional Procedure

Optional samples for COVID-19 vaccine immunological assessments:



ICF = Informed Consent Form; COVID-19 = coronavirus disease 2019.

[a] Up to three study visits (dosing or non-dosing) following completion of vaccination. Sample collection to be performed if within a period of approximately 12 months (approximately 48 weeks) since completion of vaccination. Depending on when the subject signed the ICF and vaccination was completed, one or more sample collection may not be applicable.

[b] Up to two study visits (dosing or non-dosing), within *approximately* 6 months (approximately 24 weeks) since the booster dose. Booster sample collection will override the schedule of previous post-vaccination sample collection. Depending on when the subject signed the ICF and vaccination was completed, one or more sample collection may not be applicable.

[c] Not applicable for vaccines approved as a single dose.

[d] Samples to be collected only after one booster dose. If additional booster doses are provided during the duration of the study, the sample is not to be collected.

[e] ICF can be signed up to the collection of the first sample or up to 6 months or 12 months (whichever comes first) following the last vaccine dose. In case of a booster dose, the ICF can be signed up to the collection of the first sample or up to 6 months following the booster dose.

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 the schedule of assessments (see Appendix 1, Appendix 2, and Appendix 3).

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.

Pregnant and breastfeeding patients 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. Please refer to Section 4.3.2.3.

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, and Appendix 3). 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, provided that they meet the retreatment criteria. At the delayed dosing visit, additional tests or assessments, such as routine safety laboratory tests, may be performed as clinically indicated. A minimum interval of 22 weeks should be maintained between the delayed dose and subsequent dose. However, if the second infusion of Dose 1 (i.e., infusion Day 15) happens to be delayed, a minimum interval of 20 weeks should be kept between this infusion and the next infusion of Dose 2 (Week 24).

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. EDSS, 9-HPT, T25FWT, and SDMT should be performed by the Examining Investigator (or their designee, as applicable) within 7 days from the onset of a new or worsening neurological event (including relapses), in addition to completing the appropriate eCRF. Please also refer to Section 4.5.5.

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 or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient (for example, lack of efficacy)

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

- Life-threatening (NCI CTCAE Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Develop active hepatitis B infection, either new onset or reactivation
- PML
- Patient's decision to discontinue the treatment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced and will stay in *the* double-blind phase until the primary analysis.

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

During the Double-Blind Treatment phase, patients who prematurely discontinue from study drug treatment will continue the Double-Blind Treatment assessments. After treatment discontinuation, every effort should be made to have the patient continue the study assessments in the treatment phase of the study (DBT), despite the fact that they are not receiving the actual study treatment (See also Section 3.1 on the study setup).

During the Open-Label Extension phase, patients who prematurely discontinue from study drug treatment and withdraw from the OLE phase should return to the clinic for a treatment discontinuation visit (see Appendix 2 for additional details).

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

4.7.2 Patient Withdrawal from the Study

If a patient withdraws from the study during the Double-Blind Treatment or Open-Label Extension phases, the patient will return to the clinic for a treatment discontinuation visit.

If a patient withdraws from the study during the Safety Follow-Up or B-Cell Monitoring phases, patients will return to the clinic for an end of observation or withdrawal from follow-up visit (see Appendix 3 for additional details).

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.

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.

If a patient withdraws 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 the medical record. 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 Termination by Sponsor

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 Closure

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 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. This also includes prior experience with doses above 600 mg in both MS (Phase II [Study WA21493]) and RA (Phase I/II and III studies), which is summarized in Appendix 11. 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 treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Ocrelizumab

5.1.1.1 Identified Risks and Adverse Drug Reactions

5.1.1.1.1 Infusion–Related Reactions

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

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

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

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

5.1.1.1.2 Infections

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

During the controlled period of the pivotal trials, the proportion of patients with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the interferon 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 RA treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the ocrelizumab IB.

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

In interventional clinical studies, there were no reports of hepatitis B reactivation in patients with MS treated with ocrelizumab, but one reported in a patient with RA 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.

When adjusting the rates of serious infections in RA for various risk factors (geographical region, gender, age, use of steroids and/or methotrexate, levels of IgM, and neutrophils) and predicting the rates of serious infections in a MS population with baseline characteristics as observed in the OPERA studies (such as younger average

age, no use of steroids or methotrexate, no patients from Asia), no dose dependent increase in serious infections rate in MS up to 1000 mg is expected (Figure 11A-1 in Appendix 11).

For PML see "Potential risks" below, Section 5.1.1.2.

5.1.1.1.3 Impaired Response to Vaccination

After treatment with ocrelizumab 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 raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the IB. At this point it is not known whether the immunization response will be impaired differently by the higher dose of ocrelizumab.

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Vaccination with live 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 (refer to Section 4.4.4).

5.1.1.1.4 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.

5.1.1.1.5 Serious Infections Related to Decrease in Immunoglobulins (Particularly in Patients Previously Exposed to Immunosuppressive/ Immunomodulatory Drugs or with Pre-existing Hypogammaglobulinaemia)

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

5.1.1.1.6 Delayed Return of Peripheral B-Cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B-cells in blood by 14 days post-treatment (first time point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow-up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients of 600 mg ocrelizumab group indicates that the median time to repletion (returned to baseline/LLN, whichever occurred first) of B-cells was 72 weeks (range 27−175 weeks). At this point it is not known whether median time to repletion of B-cells will be longer for higher dose ocrelizumab.

5.1.1.2 Potential Risks

5.1.1.2.1 Progressive Multifocal Leukoencephalopathy

*JC virus infection resulting in p*rogressive multifocal leukoencephalopathy (PML) has been reported in patients *treated with anti CD-20 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 a risk of PML cannot be ruled out, p*hysicians 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 a PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, *preferably with contrast (compared with pre-treatment MRI),* confirmatory CSF testing for JC Viral DNA, and repeat neurological assessments should be considered. If a PML is confirmed, ocrelizumab must be discontinued permanently. Refer to Appendix 9 for guidance for diagnosis of PML. Also refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.1.2.2 Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although 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.

5.1.1.2.3 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 0 of 668 females treated with interferon 1α or placebo.

Patients should follow standard breast cancer screening guidelines. Refer to the Ocrelizumab Investigator's Brochure for more details.

5.1.1.2.4 Neutropenia

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

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).

Female patients who become pregnant during the study will continue with the study assessments as per SoA (unless an assessment is contraindicated in pregnancy [e.g., MRI]) however, 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

5.1.4.3.1 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, study treatment may need to be discontinued. Refer to ocrelizumab local label for further guidelines.

Handling of IRRs will depend on the intensity of symptoms and shall not depend on the dose administered (see also Table 7 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 discontinued from study treatment.

The above examples of infusion 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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A SAE is any AE that meets any of the following criteria:

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

  This does not include any AE 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 AE 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 National Cancer Institute Common Terminology Criteria for Adverse Events [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 AE recorded on the eCRF.

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

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

Adverse events of special interest (AESI) 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). AESI 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 AE eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–Section 5.6.

For each AE recorded on the AE 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 AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the AE eCRF.

After informed consent has been obtained but prior to initiation of study drug, only SAEs 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 AEs will be reported throughout the study duration.

Instructions for reporting AEs that occur after the AE 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 AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 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 SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE 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 AE 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 8):

- 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 8 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., pre-existing 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 AE eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the AE eCRF.

5.3.5.1 Infusion-Related Reactions

AEs 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 AE eCRF). If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated IRR eCRF.

5.3.5.2 Diagnosis Versus Signs and Symptoms

For AEs other than IRR (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the AE 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 AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE 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, AEs 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 AE that is separated in time from the initiating event should be recorded as an independent event on the AE 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 AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the AE eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the AE 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 AE 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 SAEs.

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., 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 AE.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE 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 AE. 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 AE eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.6 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., 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 AE.

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 AE eCRF.

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

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 AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times ULN$ in combination with total bilirubin $>2\times$ULN (of which $\geq$35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times ULN$ in combination with clinical jaundice

The most appropriate diagnosis (if a diagnosis cannot be established) of the abnormal laboratory values should be recorded on the AE 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 SAE or an AESI (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the AE 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 AE 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 AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of MS, "Multiple Sclerosis progression" should be recorded on the AE eCRF.

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

5.3.5.9 Pre-existing Medical Conditions

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

5.3.5.10 Lack of Efficacy or Worsening of Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on components of cCDP: EDSS scores and/or T25FWT scores and/or 9-HPT times (Section 2.1.1). 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 AE.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious AE (per the definition of SAE 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 AE or a SAE:

- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones, and diagnostic testing. Such events should still be recorded as medical procedures in the concomitant procedures/treatments eCRF.
- Hospitalization to receive trial medication such as infusions of ocrelizumab unless this is prolonged (more than 24 hours).
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with IV methylprednisolone

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

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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves AEs but may result in AEs. Each AE associated with a special situation should be recorded separately on the AE eCRF. If the associated AE fulfills seriousness criteria, 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, AEs associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with ocrelizumab, regardless of whether they result in an AE, should be recorded on the AE 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 AE 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.

5.3.5.13 Patient-Reported Outcome Data

AE reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for AEs.

5.3.5.14 Safety Biomarker Data

AE reports will not be derived from 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.

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:

- SAEs (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- AEs of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For SAEs and AESI, the investigator must report new significant follow-up information 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 SAEs to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. To ensure the safety of study patients, an Emergency Medical Call Center will be available

24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to 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 SAEs 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, SAEs and AESI will be reported until 48 weeks after the final dose of study drug but may be extended in patients whose B cells take longer to replete. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the AE eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial *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 serious AEs that occur >48 weeks after the final dose of study treatment 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 AE eCRF but in dedicated eCRF form. The investigator should *suspend all infusions of* study drug *until completion of the pregnancy and breastfeeding* and counsel the patient,

discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs 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 AE 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. In parallel, dedicated eCRF form should be updated accordingly. Information regarding child health up to 1 year should be collected on the infant health questionnaire (see Appendix 10), if approved by IRB/EC and, if applicable, an appropriate regulatory body and consented by the patient.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a SAE (as the Sponsor considers abortions to be medically significant), recorded on the AE 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 AE, recorded on the AE 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 AE.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form and on the dedicated eCRF 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 AE, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE 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 AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE 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, if approved by IRB/EC and, if applicable, an appropriate regulatory body and consented by the patient.

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious AE that occurs after the end of the AE reporting period (defined as during the study), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the AE 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

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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 authorities (which includes the use of applicable systems, such as EudraVigilance), Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events through 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. An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

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 *(SAP)*, which will be finalized prior to the database lock and unblinding. *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 sample size was determined based on data from Studies WA21092 and WA21093 (Opera I & Opera II) and Kappos and colleagues (2018). A two-group test of equal exponential survival curves was used to determine the sample size for the time to 12-week cCDP. With the 2:1 randomization ratio between the higher dose treatment arm and approved dose treatment arm and assuming recruitment of 390 patients per year, 5% annual dropout rate, a control group progression rate of 21.5% and 5% two-sided Type I error, the sample size of approximately 786 (524:262) patients will be required to observe 205 events and achieve 80% power to detect the hazard ratio of 0.66. The double-blind treatment period phase will run until at least 205 12-week cCDP events are observed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Intercurrent events 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, and 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.

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.

For analysis purposes, treatment discontinuation will be defined as 24 weeks after the last dose.

6.4.1 Primary Efficacy Endpoint

Primary Estimand: The trial will compare the higher dose of ocrelizumab with the approved dose of ocrelizumab in patients with RMS.

The primary efficacy objective is to demonstrate superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab as assessed by risk reduction in cCDP sustained for at least 12 weeks.

The comparison of interest is the difference in time from randomization to cCDP12 between treatment arms, as expressed by the hazard ratio. The primary comparison will be made regardless of adherence to the randomized treatment or use of an approved MS DMT medication.

Time to onset of cCDP is defined as the first occurrence of a confirmed progression event according to at least one of the following three criteria:

- CDP, or
- a sustained increase of $\geq$20% from baseline in T25FWT score, or
- a sustained increase of $\geq$20% from baseline in 9-HPT score.

As per Section 2.1.1, CDP is defined based on the EDSS. 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 T25FWT and 9-HPT scores are calculated as described in the MS functional composite guide (National Multiple Sclerosis Society 2001).

The score for the timed T25FWT is the average of the two completed trials. The most recent timed T25FWT score measured prior to randomization will be considered as baseline.

The score for the 9-HPT is an average of the four trials. The two trials for each hand are averaged, converted to the reciprocal of the mean time for each hand, and then two reciprocals are averaged and back-transformed to the original scale (i.e., by taking another reciprocal). The most recent 9-HPT score measured prior to randomization will be considered as baseline.

Assessments collected within 30 days from PDR will not be used for the confirmation of cCDP (see Section 4.5.5.2 for more details on the definition of PDR).

In order to estimate the treatment effect targeted by the primary estimand the following intercurrent event (IE) handling strategies will be applied:

Treatment discontinuation: every effort will be made to collect the data post-IE until the primary analysis. All available data will be included in the analysis following the treatment-policy strategy.

Initiation of an approved MS DMT medication: every effort will be made to collect the data post-IE until the primary analysis. All available data will be included in the analysis following the treatment-policy strategy.

Death: this IE is anticipated to be very rare, but in case of occurrence, it will be treated as disease progression and a cCDP event will be imputed at the time of IE in line with the composite strategy.

Intermediate missing assessments at scheduled visits prior to the last EDSS, 9-HPT, or T25FWT assessments will not be imputed. For patients with composite initial disability progression (cIDP) (i.e., disability progression that has not yet been sustained for at least 12 weeks), data collected at the next scheduled visit or treatment discontinuation visit will be used for the confirmation of progression.

In cases when patients withdraw from the study, their data (after withdrawal from the study) will be missing. The following missing data imputation rules will apply:

- If a patient discontinued a study drug due to lack of efficacy (LoE), a cCDP event will be imputed at their last EDSS, 9-HPT, or T25FWT assessments;
- Otherwise a patient will be censored at their last EDSS, 9-HPT, or T25FWT assessments.

Patients still on study drug and without prior cCDP event at the time of study unblinding will be censored at their last EDSS, 9-HPT, or T25FWT assessments (administrative censoring).

Primary Estimator: The hazard ratio will be estimated from a Cox proportional hazards regression, stratified by the randomization stratification factors. The statistical

significance will be assessed using the log-rank test, stratified by the randomization stratification factors.

Sensitivity analyses: In order to assess the robustness of the estimated treatment effect to the proposed missing data imputation strategy, analyses described in the primary estimator will be repeated using different imputation rules:

- For patients who had cIDP at the time of premature withdrawal from the study and who discontinued the study drug for other reason than LoE, cCDP events will be imputed for the fraction of patients. This fraction will be defined based on the observed cIDP confirmation rates in the study. If the event is not imputed, the patient will be censored at their last cCDP assessment prior to withdrawal from the study. In addition, a tipping point analysis will be performed to investigate the sensitivity of the results to the selection of the fraction of cIDP to be imputed as cCDP events.
- For all patients who prematurely withdraw from the study, it will be attempted to predict the time of cCDP event from control arm patients who stay in the study until primary analysis, but have discontinued study drug before the respective study withdrawal times. The feasibility of this imputation approach is highly reliant on the number of patients in control arm who would discontinue a study drug, but stay in the study until its completion.

Supplementary estimand: Additional treatment effect, incorporating discontinuation of the study drug due to AE into the definition of treatment benefit, will be estimated to supplement the primary estimand:

> The comparison of interest is the difference in time to cCDP12 or study drug discontinuation due to AE, as expressed by hazard ratio. The primary comparison will be made regardless of adherence to the randomized treatment or use of an approved MS DMT medication.

In order to better characterize the treatment effect derived using cCDP, additional supplementary analyses will be performed to examine contribution of its individual components. Further supplementary analyses may be performed and all details will be pre-specified in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy objective is *twofold. First,* to demonstrate superiority of a higher dose of ocrelizumab over the approved dose of ocrelizumab on the basis of the endpoints listed in Section 2.1.2. *Second, to demonstrate that both the higher dose and standard dose of ocrelizumab can lead to a significant reduction in NfL from baseline on the basis of the endpoints listed in Section 2.1.2*

Secondary estimands: For all time to event endpoints, the comparison of interest is the difference in time to event between treatment arms, as expressed by the hazard ratio.

For all other endpoints, *with the exception of the NfL endpoints,* the comparison of interest is the difference in variable means between treatment arms. *For the NfL endpoints, the comparisons are the change from baseline at Week 48 within each treatment arm.*

All comparisons, except for the MRI *and NfL* endpoint*s* (*e.g.*, the change in brain volume), will be made regardless of adherence to the randomized treatment or use of an approved MS DMT medication (treatment-policy strategy). For the MRI *and NfL* endpoint*s*, the comparison will be made as if no treatment discontinuation or switch to an approved MS DMT medication has occurred (hypothetical strategy).

If primary estimand is statistically significant, all secondary estimands will be tested in a fixed sequence at 0.05 significance level. The sequence of hierarchical testing will be specified in the SAP.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy objective for this study is to evaluate the efficacy of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab on the basis of, endpoints described in Section 2.1.3.

The analysis of exploratory efficacy endpoints will be described in the SAP.

6.4.4 Subgroup Analyses

Subgroup analyses will be performed for primary and secondary estimands. Subgroups will be defined based on the following parameters:

- Randomization stratification factors
- Presence or absence of T1Gd+ lesions
- T2 lesion count (the exact categories will be specified in the SAP)
- Duration since MS symptoms onset ($\leq$3 years, 3 to $\leq$5 years, 5 to $\leq$10 years, $>$ 10 years)

Any further subgroup analyses will be specified in the SAP.

6.5 SAFETY ANALYSES

The safety objective for this study is to evaluate the safety profile of a higher dose of ocrelizumab compared with the approved dose of ocrelizumab as well as the overall safety profile and safety profile over time, on the basis of endpoints listed in Section 2.2.

All patients who received at least one infusion (partial or complete) of study drug with patients grouped according to actual treatment received will be included in the analysis.

- The safety data will be summarized regardless of premature study treatment discontinuation or switch to an approved MS DMT medication (including commercial ocrelizumab).

- Additionally, the safety data may also be summarized regardless of premature study treatment discontinuation but until switching to an approved MS DMT medication (including commercial ocrelizumab).

6.5.1 Analyses of Exposure, Adverse Event, Laboratory and Vital Sign Data

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim AE terms will be mapped to MedDRA thesaurus terms, and AE severity will be graded according to NCI CTCAE v5.0. All AEs, SAEs, AEs leading to death, AESI, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory and vital sign (pulse rate and blood pressure) data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

The PK objective for this study is to assess the exposure to ocrelizumab in serum in all patients in both study arms, and to evaluate a potential relationship between drug exposure and the efficacy and safety of ocrelizumab.

Non-linear mixed effects modeling will be used to analyze the sparse 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 which may interfere with PK evaluation. The PK data of this study may be pooled with data from other studies. Population PK parameters (clearances and volumes) will be estimated and the influence of covariates, such as age, gender, weight, ADA, and baseline CD19 B-cell count will be investigated. Further PK analyses may get conducted as appropriate.

The PK analysis may get reported separately from the main study CSR.

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 (post-baseline incidence) will be summarized by treatment group. When determining post-baseline 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 post-baseline 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 post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline 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 may be analyzed and reported descriptively.

6.8 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Biomarkers will be presented as absolute value over time and/or percent change relative to baseline 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. Samples taken at screening and baseline before first ocrelizumab dose may be averaged to better normalize post-dose endpoints taking into account normal variability.

6.9 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.10 SARS-COV-2 VACCINATION ANALYSES

Immunology analyses of SARS-CoV-2 antibody titers and SARS-CoV-2 T-cell responses will be conducted as appropriate, and details will be specified in a separate Biomarker Analysis Plan.

6.11 INTERIM ANALYSES

6.11.1 Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct interim efficacy analysis and/or interim futility analysis.

If interim analyses are conducted, the Sponsor will remain blinded. The interim analyses will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct the optional interim analyses, along with the rationale, timing, and statistical details for the analyses, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analyses. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analyses (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below the specified threshold, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter.

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 for all patients screened. 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 COAs, 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.

COAs 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 for all patients screened 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 AND CLINICIAN REPORTED AND PERFORMANCE OUTCOME DATA

An electronic device will be used to capture COAs data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.
All instruments apart from EDSS will have a web-based back-up option if required, from study start. EDSS will have a paper back-up option from study start and a web-based option is envisaged for a later stage

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 that must be kept with the study records as source data.

Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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 COAs data (if applicable), ICFs, laboratory

test results, imaging data, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States 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 E.U. Clinical Trials Directive (2001/20/EC)*, or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs such as an 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 ICF 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 ICF 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, as locally applicable. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative, as locally applicable, must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative, as locally applicable. 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 ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the

requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting serious AEs 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 ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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 genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data

may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

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, ICFs, 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. 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., AE 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.

Approximately 220 sites globally will participate to enroll approximately 786 patients. Enrollment will occur through an IxRS.

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

Additional external partners will be used for certain exploratory research that may be conducted to support future research (e.g., MRI spine sequences).

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, 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 made available 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 [aa]		1			2		3		4		5		6		N[d]			
Visit	1	2 (BL)	3	4	5	6	7	8	9	10	11	12	13	n[d]	N			
Study week		0	2	12	24	36	48	60	72	84	96	108	120	n	n+12 wks			
(Window in days)	–42 to -1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5			
Informed consent [e]	x																	
Review of eligibility criteria	x	x																
Demographic data	x																	
Medical history and baseline conditions	x																	
PROs (Neuro-QoL UE, MSIS-29, MFIS, MSWS-12, PGI-S) [f]	x	x			x		x		x		x		x		x			x
PGI-C, PGI-C-UL [f]					x		x		x		x		x		x			x
EQ-5D-5L [f]		x			x		x		x		x		x		x			x
Vital signs [g]	x	x	x	x	x		x		x		x		x		x	x		
Weight	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		
Height	x																	
Physical examination [h]	x	x			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	x
9-HPT [j]	x	x		x	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	x		x	x
T25FWT	x	x		x	x	x	x	x	x	x	x	x	x	x	x		x	x
SDMT		x		x	x	x	x	x	x	x	x	x	x	x	x		x	x
Hematology, chemistry, urinalysis [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x			x

Appendix 1:Schedule of Activities: Double-Blind Treatment

	Screen	Double-Blind Treatment														Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose [aa]		1			2		3		4		5		6		N[d]			
Visit	1	2 (BL)	3	4	5	6	7	8	9	10	11	12	13	n[d]	N			
Study week		0	2	12	24	36	48	60	72	84	96	108	120	n	n+12 wks			
(Window in days)	–42 to -1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5			
Flow cytometry (including CD3/4/8/19 count) [m]	x	x	x		x		x		x		x		x		x	x		x
CD4				x		x		x		x		x		x				
IgG, IgA, IgM	x	x		x		x		x		x		x		x				x
Pregnancy test (females) [n]	x	x	x		x		x		x		x		x		x	x		
FSH level (if applicable) [o]	x																	
Review of retreatment criteria		x	x		x		x		x		x		x		x	x		
Pretreatment with IV methylprednisolone and antihistaminic [p]		x	x		x		x		x		x		x		x	x		
Administration (infusion) of ocrelizumab (approved/higher dose) [q]		x	x		x		x		x		x		x		x	x		
Concomitant medications [r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MRI [t]	x				x		x				x		x		(x)[t]			x
ADA sample (serum) [u]		x			x		x		x		x		x		x			x
PK sample (serum) [v]		x	x	x	x	x	x	x	x	x	x		x		x			x
Biomarker plasma samples [w]		x	x	x	x		x		x		x		x		x		x	x
Biomarker serum samples [w]		x	x	x	x		x		x		x		x		x		x	x
DNA genotyping sample [x]		x																

Appendix 1:Schedule of Activities: Double-Blind Treatment

	Screen	Double-Blind Treatment														Delayed Dosing Visit[a]	Unschd. Visit[b]	Tx Discon. Visit[c]
Dose [aa]		1			2		3		4		5		6		N[d]			
Visit	1	2 (BL)	3	4	5	6	7	8	9	10	11	12	13	n[d]	N			
Study week		0	2	12	24	36	48	60	72	84	96	108	120	n	n+12 wks			
(Window in days)	–42 to -1		±2	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5			
RBR RNA Paxgene sample (optional) [y]		x	x	x	x		x		x		x		x		x		x	x
RBR Plasma sample (optional) [y]		x	x	x	x		x		x		x		x		x		x	x
RBR DNA sample (optional) [y]		x																
Hepatitis B screening [z]	x																	
HBV DNA [z] (if required)				x	x	x	x	x	x	x	x	x	x	x	x			x
Optional *plasma* and serum samples for COVID-19 vaccine immunological assessments [bb]	Please see Figure 2 for details.																	

9-HPT=9-Hole Peg Test; AE=adverse event; BL=baseline; COVID-19=coronavirus disease 2019; CSF=cerebrospinal fluid; DBT=double-blind treatment; Discon.=discontinuation; EC=Ethics Committee; eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=Informed Consent Form; IRB=Institutional Review Board; MFIS=Modified Fatigue Impact Scale; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSIS-29=Multiple Sclerosis Impact Scale–29; MSWS-12=Multiple Sclerosis Walking Scale 12-item; N=dosing visit; n=non-dosing visit; Neuro-QoL UE=Quality of Life in Neurological Disorders Upper Extremity Function; PCR=polymerase chain reaction; PGI-S=Patient Global Impression of Severity; PGI-C=Patient Global Impression of Change; PGI-C-UL=Patient Global Impression of Change of Upper Limb; PK=pharmacokinetic; PML=progressive multifocal leukoencephalopathy; PRO=patient-reported outcome; RBR=Research Biosample Repository; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; Screen.=screening; SDMT=Symbol Digit Modalities Test; SoA=schedule of activities; T25FWT=Timed 25-Foot Walk Test; Tx=treatment; Unschd.=unscheduled; WGS=whole genome sequencing; wks=weeks; (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.

[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 continue in the DBT schedule of assessments, without receiving study treatment. In case they withdraw from the study (at same time or at a later stage), they will return to the clinic for a treatment discontinuation visit.

[d] The double-blind treatment phase can be terminated at any time up to the date at which the last data point that is required for the primary efficacy analysis, as defined in the Statistical Analysis Plan, is received from the last patient. The assessments required for n and N represent the typical schedule of assessments for the double-blind treatment phase. If the patient must be discontinued from study treatment, the patient will continue in the DBT schedule of assessments. If the study ends for any reason or if the subject withdraws from the study during double-blind treatment phase, 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: MSIS-29, PGI-S, PGI-C, Neuro-QoL UE, PGI-C-UL, MSWS-12, MFIS, and EQ-5D-5L. Questionnaires will be completed every 24 weeks during the double-blind treatment phase. EQ-5D-5L will not be completed at screening. PGI-C-UL and PGI-C will not be completed at screening and baseline.

[g] Includes pulse rate, 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. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or equivalent) infusion and antihistamines. In addition, vital signs should be obtained immediately prior to the ocrelizumab infusion, then every 15 minutes (±5 minutes) for the first hour, followed by every 30 minutes (±10 minutes) for the remaining of the infusion, at the end of the infusion, and then 30 minutes (±10 minutes) and 1 hour (±10 minutes) after the end of the infusion. 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 AE 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 (if indicated), 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 AE 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, 9-HPT, T25FWT, and SDMT 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 (see Appendix 9). A patient with confirmed PML should be discontinued from the study treatment.

[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, sodium. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, and blood), and a microscopic examination if abnormal and clinically significant to 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, to be collected prior to the IV methylprednisolone infusion. This tube will be assessed at the central laboratory for TBNK (B-cell count), high-sensitivity B-cell assay, and B-cell subset assays.

[n] All women of childbearing potential will have a serum pregnancy test at screening analyzed by the central laboratory. Urine pregnancy tests (Urine β-hCG sensitivity of at least 25 mU/mL) will be performed at the local laboratory 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 at the central laboratory.

[o] 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.

[p] Patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent) IV 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) prior to ocrelizumab 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. Treatment with the first study drug infusion should occur within 24 hours of randomization (in exceptional cases within 48 hours of randomization provided that the Investigator assures that all inclusion and exclusion criteria are still met on the day of dosing). If for logistical reasons the ocrelizumab infusion at Week 24, 48, 72, 96, or any further infusion thereafter 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. Whenever possible, infusion bags should be prepared on the day of the infusion administration.

[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.

[s] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE 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 AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[t] At screening, a MRI scan will be performed at least 10 days before the baseline visit to ensure sufficient time for central read to be performed for eligibility. After enrolment, MRI scans should occur within ±4 weeks of the scheduled visits. In addition, MRI scans will be obtained in patients who *withdraw from the* study (at *the* treatment discontinuation visit) if one was not performed during the prior 4 weeks. From Week 120 onward, MRI scans will be performed every 48 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, for pre- and post-dose. In the case that would not be possible, at least the post-dose sample should be collected from the arm opposite to the infusion, to avoid contamination.

[w] At infusion visits, plasma and serum samples for biomarkers will be collected prior to the IV methylprednisolone as indicated.

[x] 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, collection of this sample will not be applicable at that site.

[y] 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 (Paxgene) and an RBR plasma sample collected prior to the IV methylprednisolone infusion at all indicated visits.

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

[aa] In case of a dose delayed (e.g., due to COVID-19 impact, safety events), the next dose has to be scheduled 24 weeks following the delayed dose, with a minimum of 22 weeks interval between these 2 doses. If the second infusion of Dose 1 (i.e., infusion Day 15) happens to be delayed, the next dose has to be scheduled 22 weeks following the delayed dose, with a minimum interval of 20 weeks between this infusion and the next infusion of Dose 2.

[bb] *Plasma* and serum samples collected on the day of the infusion must be collected prior to the IV methylprednisolone (or equivalent) administered as premedication. Samples will be collected before vaccination (if patient signs the ICF before receiving a vaccine dose) and/or up to 12 months following completion of vaccination (matching the visit closest to 12 months following completion of vaccination), to a maximum of three visits (visit closest to completion of vaccination, and visit approximately 6 months and 12 months following completion of vaccination). In case of a booster dose, samples will be collected up to 6 months following the booster dose (matching the visit closest to 6 months following the booster dose), to a maximum of two visits (visit closest to administration of the booster dose and visit approximately 6 months after administration of booster dose). Depending on when the patient signed the ICF and vaccine doses were administered, one or more sample collection may not be applicable (refer to Section 4.5.12).

Appendix 2
Schedule of Activities: Open-Label Extension

	OLE Screening	OLE								Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose [w]		1		2		3		4				
Visit		1	2	3	4	5	6	7	8			
Study week		Wk 0	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	Wk 72	Wk 96			
(Window in days)	–30 to –1		(±7)	(±5)	(±7)	(±5)	(±7)	(±5)	(±5)			
Informed consent [d]	x											
Review of eligibility criteria	x	x										
PROs (Neuro-QoL UE, MSIS-29, MFIS, MSWS-12, PGI-C, PGI-C-UL, PGI-S, EQ-5D-5L) [e]		x				x			x			x
Vital signs [f]		x		x		x		x	x	x		
Weight	x	x	x	x	x	x	x	x		x		
Physical examination [g]		x		x		x		x	x	x		x
Neurological examination [h]		x	x	x	x	x	x	x	x		x	x
9-HPT [i]		x		x		x		x	x		x	x
EDSS [j]		x		x		x		x	x		x	x
T25FWT		x		x		x		x	x		x	x
SDMT		x		x		x		x	x		x	x
Hematology, chemistry, urinalysis [k]	x	x	x		x		x		x			x
Flow cytometry (including CD3/4/8/19 count) [l]		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) [m]	x	x		x		x		x		x		
FSH level (if applicable)[n]	x											
Review of re-treatment criteria		x		x		x		x		x		
Pretreatment with IV methylprednisolone and antihistaminic [o]		x		x		x		x		x		

	OLE Screening	OLE								Delayed Dosing Visit [a]	Unschd. Visit [b]	Tx Discon. Visit [c]
Dose [w]		1		2		3		4				
Visit		1	2	3	4	5	6	7	8			
Study week		Wk 0	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	Wk 72	Wk 96			
(Window in days)	–30 to –1		(±7)	(±5)	(±7)	(±5)	(±7)	(±5)	(±5)			
Administration (infusion) of ocrelizumab (higher dose) [p]		x		x		x		x		x		
Concomitant medications [q]	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
MRI (every 48 weeks) [s]		(x)		(x)		(x)		(x)	(x)			x
ADA sample (serum) [t]		x				x						x
Biomarker plasma sample [u]		x				x			x		x	x
Biomarker serum sample [u]		x				x			x		x	x
HBV DNA (if required) [v]	x	x	x		x		x		x			x

9-HPT=9-Hole Peg Test; ADA= anti-drug antibody; AE=adverse event; COVID-19=coronavirus disease 2019; Discon.=discontinuation; eCRF=electronic Case Report Form; EDSS=Expanded Disability Status Scale; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; FSH=follicle stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; MFIS=Modified Fatigue Impact Scale; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSIS-29=Multiple Sclerosis Impact Scale–29; MSWS-12=Multiple Sclerosis Walking Scale-12 item; Neuro-QoL UE=Quality of Life in Neurological Disorders Upper Extremity Function; OLE=open-label extension; PCR=polymerase chain reaction; PGI-C=Patient Global Impression of Change; PGI-C-UL=Patient Global Impression of Change of Upper Limb function; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetic; PML=progressive multifocal leukoencephalopathy; PRO=patient reported outcome; SDMT=Symbol Digit Modalities Test; T25FWT=Timed 25-Foot Walk test; Tx=treatment; Unschd.=unscheduled; 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.

[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.

[d] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[e] 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: MSIS-29, PGI-S, PGI-C, Neuro-QoL UE, PGI-C-UL, MSWS-12, MFIS, and EQ-5D-5L .

[f] Includes pulse rate, 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. On ocrelizumab infusion visits, vital signs should be taken within 45 minutes prior to the methylprednisolone (or equivalent) infusion, and antihistamines, immediately prior to the ocrelizumab infusion and 1 hour (±10 minutes) after the end of the infusion. *In the event of an IRR, in addition to the timepoints above, vital signs should also be recorded every 15 minutes (±5 minutes) in the first hour after the onset of the IRR, followed by every 30 minutes (±10 minutes) until 1 hour (±10 minutes) after the end of the infusion.* 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 AE eCRF.

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

[h] 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, 9-HPT, T25FWT, and SDMT 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 discontinued from the study treatment.

[i] 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).

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

[k] 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, and blood) and a microscopic examination if abnormal and clinically significant to be performed at the site (local laboratory).

[l] B cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry, to be collected prior to the IV methylprednisolone infusion. This tube will be assessed at the central laboratory for TBNK (B-cell count), high-sensitivity B-cell assay, and B cell subset assays.

[m] Urine pregnancy tests (sensitivity of at least 25 mU/mL) will be performed locally 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 at the central laboratory.

[n] 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.

[o] Patients will receive prophylactic treatment with 100 mg of methylprednisolone (or equivalent) IV 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) 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. If for logistical reasons the ocrelizumab 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. Whenever possible, infusion bags should be prepared on the day of the infusion administration.

[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 AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE 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 AEs 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, MRI scans will be obtained in patients who discontinued from study treatment (at treatment discontinuation visit) if one was not performed during the prior 4 weeks. During the OLE, MRI 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] At infusion visits, plasma and serum samples for biomarkers will be collected prior to the IV methylprednisolone infusion at indicated timepoints.

[v] For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be repeated every 24 weeks.

[w] In case of a dose delayed (e.g., due to COVID-19 impact, safety events), the next dose has to be scheduled 24 weeks following the delayed dose, with a minimum of 22 weeks interval between these 2 doses.

Appendix 3
Schedule of Activities: Safety Follow-Up and B-Cell Monitoring

	SFU [a]	BCM [b]	EOO or WD from SFU
Study week	Visits every 12 wks	Visits every 24 wks	
(Window in days)	(±7 d)	(±7 d)	
Physical examination [c]	x	x	x
Neurological examination [d]	x	x	x
9-HPT and T25FWT [e]			x
EDSS [f]			x
SDMT			x
Hematology, chemistry, urinalysis [g]	x	x	x
Flow cytometry (including CD3/4/8/19 count) [h]	x	x	x
IgG, IgA, IgM	x		
Concomitant medications [i]	x	x	x
Adverse events [j]	x	x	x
MRI [k]			x
HBV DNA (if required) [l]	x	x	x

9-HPT = 9-Hole Peg Test; AE = adverse event; BCM = B-cell monitoring; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; EOO = end of observation; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; T25FWT= Timed 25-Foot Walk test; WD = withdrawal; wks = weeks.

Note: All assessments should be performed on the day of the scheduled visit, unless otherwise specified.

[a] Laboratory and safety assessments performed during clinical visits every 12 weeks. All patients will continue in the SFU until the end of the SFU phase.

[b] At the end of SFU, all patients will move into BCM phase until the end of 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 AE eCRF.

[d] Neurological examinations will be used to distinguish any new or worsening neurological events (including relapse) in MS from other 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, 9-HPT, T25FWT, and SDMT assessments 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 discontinued from the study treatment.

[e] 9-HPT: 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).

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

[g] 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, and blood) and a microscopic examination if abnormal and clinically significant, will be performed at the site (local laboratory).

[h] B-cells and other cell types and/or B-cell subsets will be assessed in fresh whole blood using flow cytometry. This tube will be assessed at the central laboratory for TBNK (B-cell count).

[i] 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.

[j] All AEs will be reported for as long as the patient remains in the study. The investigator should follow each AE 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 AEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[k] MRI scans will be obtained in patients who *withdraw* from study (at WD from follow-up or EOO visit) if one was not performed during the prior 4 weeks.

[l] For those patients enrolled with negative HBsAg and positive total HBcAb, HBV DNA (PCR) must be performed.

Appendix 4
Multiple Sclerosis Impact Scale-29 (Version 2)

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

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 2

MSIS-29 - United States/English - Version of 22 Feb 13 - MAPI Institute.

Appendix 5
Modified Fatigue Impact Scale

MFIS-1

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

MFIS-2

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
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

MFIS-21 - United States/English - Mapi.
MFIS-21_AU1.0_eng-USort.doc

Appendix 6
Neuro-QoL Upper Extremity Function

Neuro-QoL Item Bank v1.0 – Upper Extremity Function (Fine Motor, ADL)

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
NOMEX44	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
NOMEX39	Are you able to cut your toe nails?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		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

Appendix 7
Multiple Sclerosis Walking Scale

Multiple Sclerosis Walking Scale (MSWS-12)

- These questions ask about **limitations to your walking** due to MS **during the past two weeks**.
- For each statement, please **circle** the **one** number that best describes your degree of limitation.
- Please answer **all** questions even if some seem rather similar to others, or seem irrelevant to you.
- **If you cannot walk at all**, please tick this box. ☐

In the past two weeks, how much has your MS ...	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (e.g. holding on to furniture, using a stick, etc)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (e.g. using a stick, a frame, etc)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

Please check that you have circled ONE number for EACH question

Appendix 8
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 9
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if Progressive Multifocal Leukoencephalopathy is Suspected

- If the clinical presentation is suggestive of PML (see Table 9A-1), further investigations should include brain MRI evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 9A-1), a lumbar puncture with evaluation of the CSF for the detection of JC virus (JCV) DNA using a validated sensitive assay should be undertaken (refer to the Lab Manual for testing details). A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007)

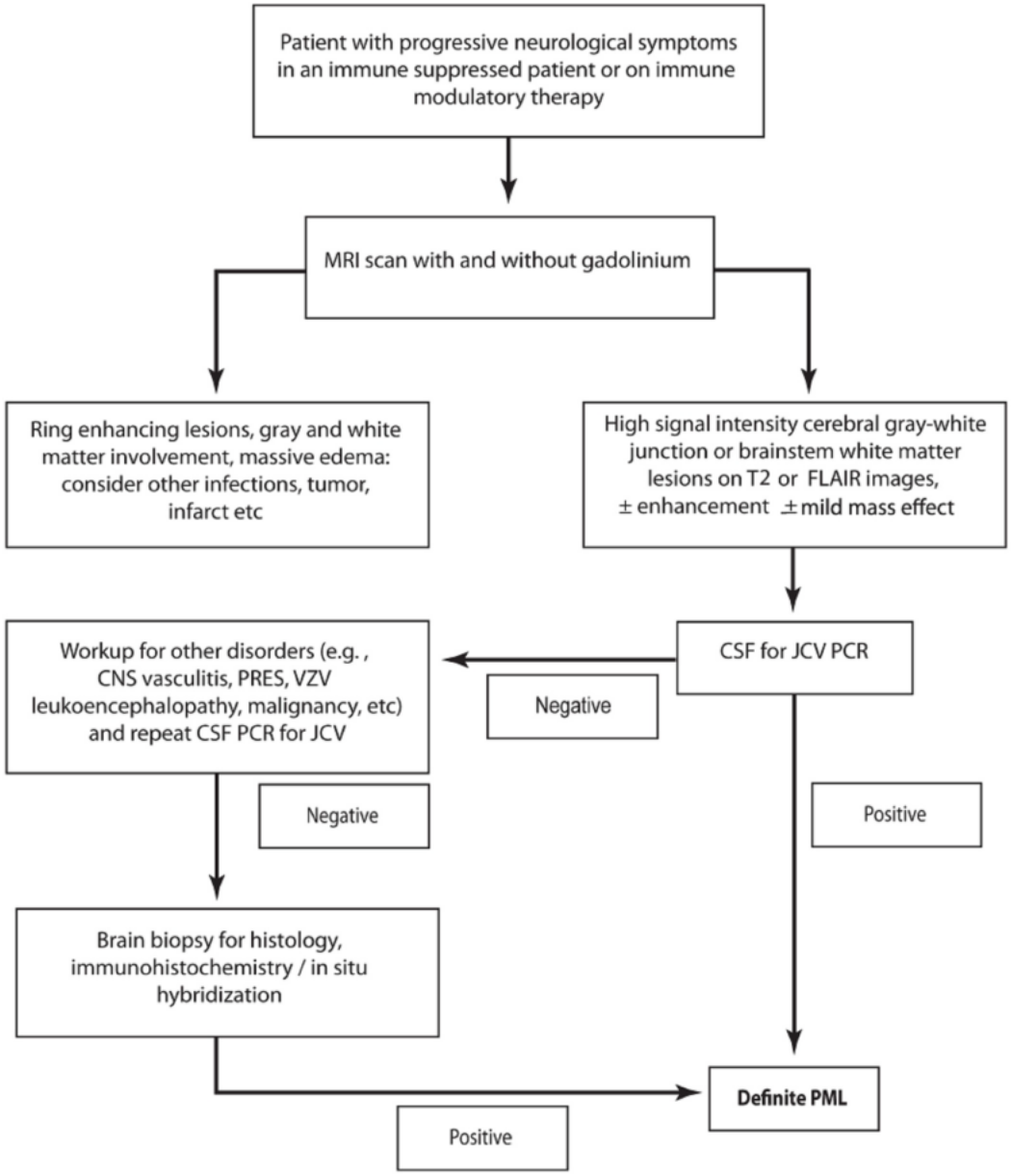
MRI Assessment

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive of PML (see Figure 9A-1).
- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 9A-1 for differences in lesion characteristics that may help differentiate between PML and MS).

CSF Assessment

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

Figure 9A-1 Diagnostic Algorithm Framework for PML



FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; VZV = varicella-zoster virus.

Source: (Berger et. al. 2013)

Table 9A-1 Clinical Signs and Symptoms Typical of MS and PML

	MS Acute	PML Subacute
Onset		
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.

Source : Adapted from Kappos et al. 2007.

Table 9A-2 MRI Lesion Characteristics Typical of PML and MS

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

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

Source: Adapted from Yousry et al. 2006.

Appendix 10
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 ☐

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

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

Table 4: Status of Infant

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

Infections in neonate and infant during first year of life

Any infection detected at birth?

☐ Yes
☐ No
☐ Unknown

If available, please provide CD19 count (B-cell values) at birth (regardless of infection). Are the results (select one option below)____?

☐ Normal
☐ Abnormal
☐ Unknown

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

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

Table 5: Information on Infection in Neonate at Birth

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

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

Maternal risk factors for neonatal infection	Date of diagnosis	If diagnosed, was pregnant mother treated with anti-infective prior to delivery?
☐Maternal intrapartum 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: _____

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

☐ Yes
☐ No
☐ Unknown

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

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

Specify the event term:	Event number (automatically populated by the system?)		
Location of infection?	Infant's age on day of onset of infection?	Outcome of infection?	Duration of infection?
Site of infection (specify): _____	Age:_____	☐Resolved ☐Improving ☐Fatal ☐Persisting ☐Unknown	Duration:___
Intensity of infection (Grade 1-5 NCI CTCAE)?	Seriousness of infection?	Treatment with anti- infective?	Pathogen causing infection known?
Severity: ☐Mild (Grade 1) ☐Moderate (Grade 2) ☐Severe (Grade 3) ☐Life-threatening (Grade 4) ☐Death (Grade 5)	Serious: ☐Yes ☐No	☐Yes, specify: _____ ☐No ☐Unknown	☐Yes (specify): _____ ☐No ☐Unknown
Relevant laboratory test results (in infant):			
CD19 count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
IgG levels	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
White blood cell count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Neutrophil count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Lymphocyte count	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____
Other, specify:	☐normal ☐abnormal ☐unknown	If abnormal, specify test result:	If abnormal, date of test: _____

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

Vaccinations administered at birth and during first year of age	Date administered	Infant's age on day of vaccination	Comments (abnormal outcome, reason for postponing vaccination, etc.)
☐Hepatitis B			
☐Rotavirus			
☐Diphtheria, tetanus, and pertussis			
☐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 11
Safety Analysis of Prior Experience with Ocrelizumab at Higher Doses

Prior experience with ocrelizumab IV doses above the approved 600 mg is available from clinical trials in MS and in RA patients, including patients receiving ocrelizumab 1000 mg, 1500 mg, and 2000 mg.

Relevant details of the results from these Clinical Study Reports, from the Pooled Phase II and Phase III RA Controlled Treatment (RA controlled treatment population) and narratives are available upon request. Key findings from these data on the important identified risks of IRR and infections are summarized below, together with the current known safety profile of ocrelizumab 600mg, the statistical analysis modelling for the Prediction of SIE rates in MS population from the RA data, and the ocrelizumab MS phase II/III exposure-safety correlation, form the basis for the proposed risks, safety assessments and safety plan described in protocol Section 5.

1 SUMMARY OF CLINICAL SAFETY RESULTS OF IRR AND INFECTION IN MS/RA STUDIES

1.1 INFUSION-RELATED REACTION

1.1.1 Summary of Results from MS/RA studies

- In the RRMS Phase II Study (WA21493), a total of 55 MS patients were randomized to 2000 mg (dual infusions of 1000 mg separated by 14 days in Cycle 1) ocrelizumab group. During the placebo-controlled 24-week period, the higher number of AEs observed in the ocrelizumab 2000 mg group (termed 1000 mg group in the study as the patients received a total dose of 2000 mg but in two infusions of 1000 mg for Cycle 1) was driven mainly by the higher number of IRRs reported during the first (Day 1) and the second infusion (Day 15) of Cycle 1. Most of the IRRs were mild to moderate (Grade 1 or 2). One severe (Grade 3) IRR occurred during the placebo-controlled period in the ocrelizumab 2000 mg group.
- In the RA Phase I/II studies (ACT2847g and WA18230), 85 patients were randomized to receive ocrelizumab 1000 mg, 45 patients to receive ocrelizumab 1500 mg, and 48 patients to receive ocrelizumab 2000 mg. The safety profile of ocrelizumab in these studies was consistent across dose groups and suggested only slight differences from placebo, except for the incidence of IRRs, which was greater in ocrelizumab-treated subjects than placebo-treated subjects. Most of the infusion-related AEs were mild or moderate in severity across all treatment groups. In study WA18230, all three doses were delivered as single infusions. A total of 45 patients received single IV infusion of ocrelizumab 1500mg and 8 patients received single infusion of 2000mg. In one of the two patients who experienced a mild to moderate IRR (with symptoms of chills, nausea, and vomiting) in the 2000 mg treatment arm, the infusion was stopped so that the patient did not receive the full infusion. The patients in these studies were not pretreated with corticosteroids prior to receiving the infusion. Prophylactic doses of acetaminophen

and diphenhydramine (or other non-sedating antihistamine), given 30–60 minutes before the infusion of ocrelizumab was initiated, were recommended, but not mandatory. In the ocrelizumab high dose studies, both methylprednisolone and an antihistamine are mandatory premedications before each infusion, and antipyretics are recommended.

1.2 INFECTIONS

1.2.1 Summary of Results from MS/RA Studies

- During the placebo-controlled 24-week period of the RRMS Phase II Study (WA21493), there was no increase in the incidence of infections in the ocrelizumab groups (600 mg and 2000 mg dose) compared with the placebo group in the RRMS Phase II study.
- In the RA Phase I/II Study ACT2847g, the incidence of any infection-related adverse events was higher in the placebo group than in the ocrelizumab group. In Phase I/II Study WA18230, the incidence of infections was similar across the placebo (13/35, 37%) and ocrelizumab 400 mg (14/43, 33%) to 1500 mg (13/45, 29%) groups. The incidence was 5/8 in the 2000 mg group, which should be interpreted with caution given the small sample size.
- The pooled analyses of safety data from the Phase II/III studies in RA demonstrated serious infections were reported more frequently in the 1000 mg dose group compared to the 400 mg dose group or immunosuppressant+placebo group. Risk factors for serious infections in these trials included other comorbidities, chronic use of steroids/immunosuppressants (including leflunomide and methotrexate), and patients from Asia. The imbalance in serious infection rate observed in RA patients is not expected with higher doses administered to MS patients, based on the following analysis:

  When adjusting the rates of serious infections in RA for various risk factors (i.e., geographical region, gender, age, use of steroids and/or methotrexate, levels of IgM and neutrophils) and predicting the rates of serious infections in a MS population with baseline characteristics as observed in the OPERA studies (such as younger average age compared to RA patients, no use of steroids or methotrexate, no patients from Asia), no dose dependent increase in serious infections rate in MS with doses up to 1000 mg is expected.

  The retrospective evaluation of safety outcomes per exposure quartiles in the RRMS Phase II and III Studies (WA21493, WA21092, WA21093) and PPMS Phase III study (WA25046) showed no exposure depended differences in the safety profile (AEs, SAEs, infections, serious infections, and IRRs) up to a C_{mean} of 83 μg/mL (See Section 2).

  The highest ocrelizumab exposure observed in patients who received 2000 mg in previous MS study was 83 μg/mL (C_{mean}). By weight adjusting, it is expected that < 1% of the study participants of

BN42082/83 would be exposed to higher exposure than previously observed with 2000 mg (i.e., $C_{mean} > 83$ µg/mL). Therefore, no dose dependent increase in serious infections rate is expected in MS patients in BN42082/83 study. This study will measure immunoglobulin levels and infection rates over time in order to determine any unexpected effects of a higher dose.

1.2.2 Pooled Analysis of Infection in Phase II and Phase III RA Controlled Treatment

RA Controlled treatment population consists of all available safety data from the seven placebo-controlled double-blind controlled treatment periods of RA studies, including safety follow-up data up to the same timepoint for those patients who withdraw early. Patients were exposed to a broad range of ocrelizumab dose levels (20 mg, 100 mg, 400 mg, 1000 mg, 1500 mg, and 2000 mg). Exposure to ocrelizumab includes the following:

- A total of 1186 patients received ocrelizumab 400 mg
- A total of 947 patients received ocrelizumab 1000 mg (given as single IV infusion of ocrelizumab 1000 mg or two separate IV 500 mg infusions given 2 weeks apart)

In RA patients, 1500 mg and 2000 mg ocrelizumab were studied in Phase I/II studies:

- A total of 45 patients received a single IV infusion of ocrelizumab 1500 mg (WA18230)
- A total of 48 patients received ocrelizumab 2000mg (given as single IV infusion of ocrelizumab 2000mg [8 patients in WA18230] or two separate IV 1000mg infusions given 2 weeks apart [40 patients in ACT2847g])

All Infections

Approximately half (51.6%; 1715 patients) of the patients from all treatment arms in RA controlled treatment population reported at least one infection. The proportion of patients experiencing an infection (includes infections coded to the SOC Infections and Infestations or any AE regardless of SOC with pathogen information provided in the CRF, or any AE for which the investigator explicitly reported that it was an infection), was similar between placebo (51.6%; 506 patients) and the ocrelizumab 400 mg (50.8%; 602 patients) treatment groups, and higher in the ocrelizumab 1000 mg treatment group (55.9%; 529 patients). The proportion of patients experiencing an infection was 31.1% (14/45) in the ocrelizumab treatment groups of 1500 mg and 45.8% (22/48) in the 2000 mg.

The rate per 100 PY of infection was 102 (95% CI: 95.8, 109) in the placebo group, compared with 110 (95% CI: 103, 116) in the ocrelizumab 400 mg group, 118 (95% CI: 111, 126) in the ocrelizumab 1000 mg group, 83 in the ocrelizumab 1500 mg group (95% CI: 49, 132) and 145 (95% CI: 99, 203) in the ocrelizumab 2000 mg group.

The majority of infections were grouped to the SOC Infections and Infestations, with very few events coded to other SOCs and detected by the broader definition. The majority of infections were of bacterial or viral origin.

The most common infections by Preferred Term, reported with a frequency of ≥5% in any of the treatment groups, were upper respiratory tract infection, followed by nasopharyngitis, urinary tract infection, bronchitis, and sinusitis. The frequency of all other common AEs were relatively balanced across groups.

The majority of infections in each treatment group were classified by the investigators as Grade 1 or 2 in intensity. Reports of Grade 3 events were higher in the ocrelizumab 400 mg (2.6%; 31 patients) and ocrelizumab 1000 mg (3.2%; 30 patients) groups, compared with placebo (1.7%; 17 patients). One Grade 3 infection was reported with 2000 mg ocrelizumab. There were two Grade 4 events (one patient each in the placebo and ocrelizumab 400 mg group), and six infections resulting in death. Two of the deaths occurred in the ocrelizumab 400 mg group and four in the ocrelizumab 1000 mg group.

Serious Infections

The proportion of patients reporting a serious infection was higher in ocrelizumab 1000 mg group (5.1% of patients; 66 events) compared with the placebo (3.4%; 36 events) and ocrelizumab 400 mg (3.8%; 52 events). No serious infections were reported for patients receiving 1500 mg or 2000 mg ocrelizumab.

The rate per 100 PY of serious infections was also higher in the ocrelizumab 1000 mg group (7.28; 95% CI: 5.63, 9.27) and ocrelizumab 400 mg group (5.18; 95% CI: 3.87, 6.79) compared with the placebo group (3.99; 95% CI: 2.79, 5.52). The rate of serious infections did not increase with subsequent ocrelizumab doses for any treatment group. The majority of serious infections were captured within the SOC of Infections and Infestations with more reported in the ocrelizumab 1000 mg group (4.9%; 46 patients) compared with the placebo (3.0%; 29 patients) and ocrelizumab 400 mg (3.6%; 43 patients) groups. There was no particular type of infection that contributed to the higher frequency in the ocrelizumab 1000 mg group.

Pneumonia was the most commonly reported serious infection and incidence was generally similar across placebo (1.0%; 10 patients), ocrelizumab 400 mg (0.7%; 8 patients), and ocrelizumab 1000 mg (1.2%; 11 patients) groups. Most of the serious infections with identified pathogen were of bacterial origin.

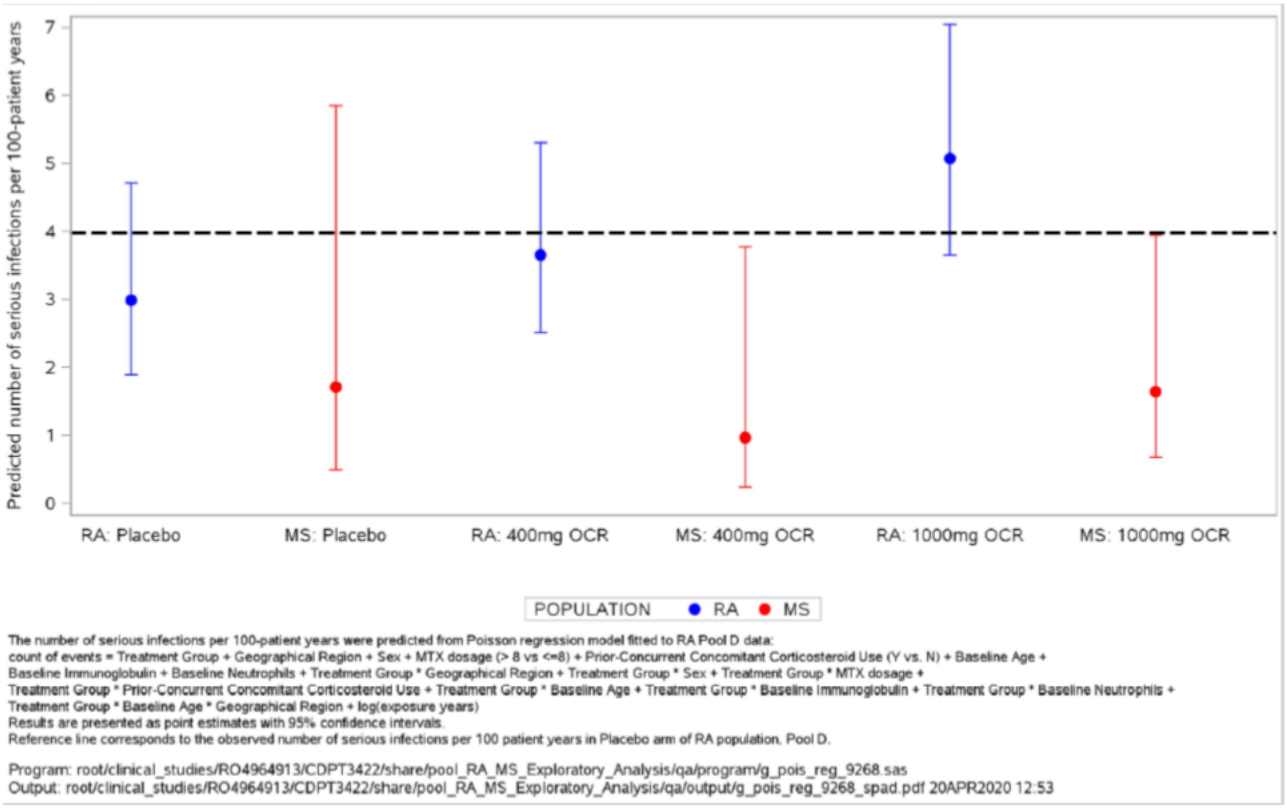
Overall, data from the RA cohort indicated that ocrelizumab treatment might increase the risk of serious infections for Asian patients/patients in Asia on chronic steroid treatment, notably on the ocrelizumab 1000 mg dose. However, these observations do not reach statistical significance and the Asian region is confounded with Asian race, lower body weight, as well as increased drug exposure.

1.2.3 Statistical Analysis Modelling for the Prediction of SIE rates in MS population from the RA Data

Additional exploratory analysis was performed to assess the risk of serious infections in the MS population based on the pooled RA data for 400 mg and 1000 mg doses. Figure 11A-1 shows that when adjusting the rates of serious infections in RA for various risk factors (geographical region, gender, age, use of steroids and/or methotrexate, levels of IgM and Neutrophils) and predicting the rates of serious infections in MS population with baseline characteristics as observed in the OPERA I and II studies (such as younger average age, no use of steroids or methotrexate, no patients from Asia), no dose dependent increase in serious infections rate in MS up to 1000 mg is expected.

Figure 11A-1: Predicted Number of Serious Infections per 100-Patient Years by Population and Treatment Arm, Pool A: Phase III RMS Controlled Treatment Population and Pool D: Phase II & III RA Controlled Treatment Population

Protocols: ACT2847G/JA21963/WA18230/WA20494/WA20495/WA20496/WA20497/WA21092/WA21093



The number of serious infections per 100-patient years were predicted from Poisson regression model fitted to RA Pool D data:
count of events = Treatment Group + Geographical Region + Sex + MTX dosage (> 8 vs <=8) + Prior-Concurrent Concomitant Corticosteroid Use (Y vs. N) + Baseline Age + Baseline Immunoglobulin + Baseline Neutrophils + Treatment Group * Geographical Region + Treatment Group * Sex + Treatment Group * MTX dosage + Treatment Group * Prior-Concurrent Concomitant Corticosteroid Use + Treatment Group * Baseline Age + Treatment Group * Baseline Immunoglobulin + Treatment Group * Baseline Neutrophils + Treatment Group * Baseline Age * Geographical Region + log(exposure years)
Results are presented as point estimates with 95% confidence intervals.
Reference line corresponds to the observed number of serious infections per 100 patient years in Placebo arm of RA population, Pool D.

Program: root/clinical_studies/RO4964913/CDPT3422/share/pool_RA_MS_Exploratory_Analysis/qa/program/g_pois_reg_9268.sas
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2 OCRELIZUMAB PHASE II/III EXPOSURE-SAFETY CORRELATION IN MULTIPLE SCLEROSIS STUDIES

Ocrelizumab Phase II/III data from the DBT period were analysed using a non-linear mixed effects model to describe ocrelizumab pharmacokinetics and assess covariate effects. Exposure-response relationships for safety parameters (SAEs, serious infections, IRRs) were assessed.

No correlation between exposure quartiles and occurrence and grade of SAE, serious infections, and occurrence and grade of IRRs was observed in patients receiving the ocrelizumab 600 mg IV regimen across both the RMS (Table 11A-1) and PPMS (Table 11A-2). Furthermore, C_{max} ocrelizumab concentrations were not higher in patients that experienced SAE compared with patients without SAE.

Table 11A-1:RMS (WA21493, WA21092, WA21093): Occurrence of Serious Adverse Events, Serious Infections, and Infusion-Related Reactions by Exposure Category for 600 mg Ocrelizumab in the Double-Blind Period

Event Type	C_{mean} Exposure	C_{mean} (µg/mL)	N patients	N patients with events	% (95% CI) patients with events
SAE	1	<15.4	210	18	8.57 (5.30–13.42)
	2	15.4–18.7	210	20	9.52 (6.06–14.53)
	3	18.7–22.2	207	10	4.83 (2.47–8.96)
	4	>22.2	208	9	4.33 (2.13–8.32)
SI	1	<15.4	210	5	2.38 (0.88–5.77)
	2	15.4–18.7	210	5	2.38 (0.88–5.77)
	3	18.7–22.2	207	2	0.97 (0.17–3.82)
	4	>22.2	208	3	1.44 (0.37–4.50)
IRR	1	<15.4	210	89	42.38 (35.66–49.38)
	2	15.4–18.7	210	67	31.9 (25.75–38.73)
	3	18.7–22.2	207	58	28.02 (22.12–34.75)
	4	>22.2	208	70	33.65 (27.36–40.57)

IRR=infusion-related reaction; SAE=serious adverse event; SI=serious infection.

Table 11A-2:PPMS (WA25046): Occurrence of Serious Adverse Events, Serious Infections, and Infusion-Related Reactions by Exposure Category in the Double-Blind Treatment Period

Event Type	C_{mean} Exposure	C_{mean} (µg/mL)	N patients	N patients with events	% (95% CI) patients with events
SAE	1	0.9–15.8	120	29	24.17 (17.03–33.00)
	2	15.8–18.9	119	19	15.97 (10.13–24.07)
	3	18.9–23.1	122	28	22.95 (16.03–31.61)
	4	23.1–48.5	121	22	18.18 (11.98–26.45)
SI	1	0.9–15.8	120	8	6.67 (3.13–13.12)
	2	15.8–18.9	119	5	4.2 (1.56–10.02)
	3	18.9–23.1	122	13	10.66 (6.02–17.86)
	4	23.1–48.5	121	6	4.96 (2.03–10.93)
IRR	1	0.9–15.8	120	47	39.17 (30.51–48.53)
	2	15.8–18.9	119	44	36.97 (28.45–46.35)
	3	18.9–23.1	122	55	45.08 (36.15–54.33)
	4	23.1–48.5	121	47	38.84 (30.25–48.16)

IRR=infusion-related reaction; SAE=serious adverse event; SI=serious infection.

A further analysis was performed to estimate the rate of serious adverse events and serious infections in each year up to the 7–8th year after randomization in the Phase III studies. The rates were estimated in the overall population and after stratifying by the C_{mean} quartiles calculated from the DBT period, as displayed in Tables 11A-1 and 11A-2. In line with the results from the DBT period, the estimated rates were not systematically higher for those in the highest C_{mean} quartile compared to those in lower C_{mean} quartiles.

Health Questionnaire

English version for the USA

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

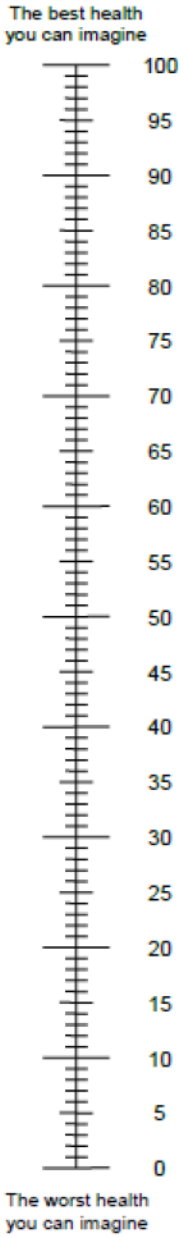
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 13
Patient Global Impression of Severity

Patient Global Impression of Severity

Please select a response below that best describes the overall severity of your MS symptoms over the past 7 days.

☐ None

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Patient Global Impression of Change

Please select a response that best describes the overall change in your MS symptoms since 6 months ago.

☐ Very much better
☐ Much better
☐ A little better
☐ The same
☐ A little worse
☐ Much worse
☐ Very much worse

Appendix 15
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 task (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 16
Exploratory Analysis to Guide Dose Selection Based on Estimating Minimum Treatment Effects

As mentioned in Section 3.3 of the protocol, lower rates of CDP were observed at higher ocrelizumab exposure quartiles in the Phase III studies in RMS (OPERA I/II: WA21092/WA201093) and PPMS (ORATORIO: WA25046), with and without adjusting for differences in patient characteristics (e.g., BMI and sex) at baseline. This indicates that a higher dose of ocrelizumab may result in better disability progression outcomes compared to the approved dose of 600 mg ocrelizumab. Given this possibility, the higher dose of ocrelizumab was chosen to maximize the probability of achieving meaningful improvements in 12-week cCDP. Specifically, the following criteria was used to guide dose selection for the current higher dose study:

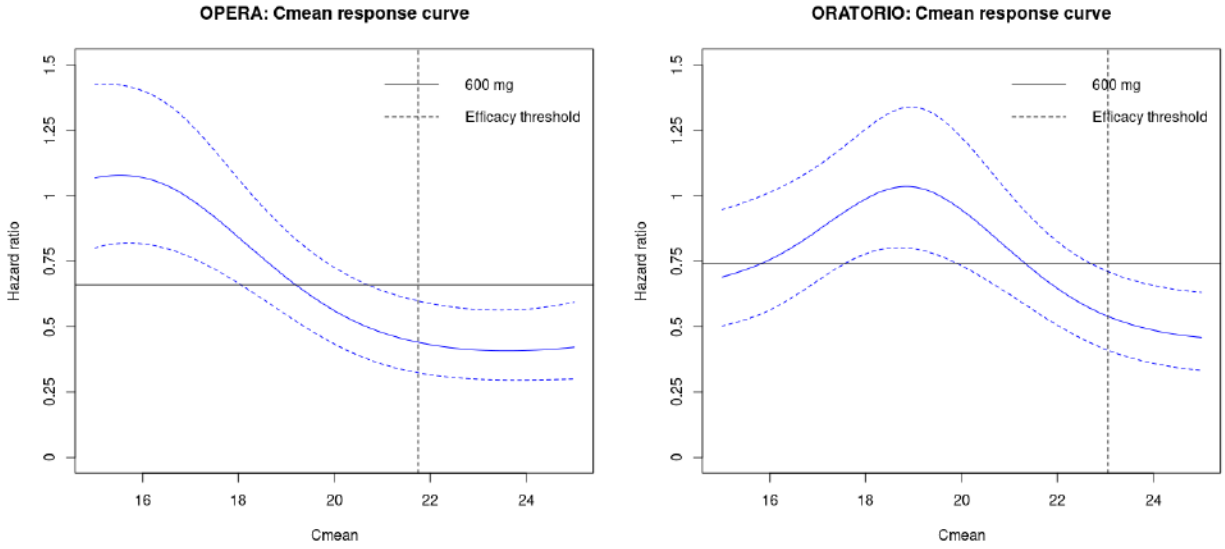
Efficacy:

- Minimum treatment effect for RMS population: ≥34% risk reduction in 12-week cCDP versus 600 mg ocrelizumab (equivalent to ≥56% risk reduction vs. Interferon [IFN]).

Observed exposure range: Minimize the proportion of patients with C_{mean} above the observed exposure range of 83 μg/mL.

The minimum C_{mean} value that all patients would need to reach in order to achieve the above-mentioned efficacy consideration was predicted using data from the OPERA I/II and ORATORIO studies. Specifically, weighted Cox Proportional hazards models were fitted to time to cCDP sustained for 12 weeks with spline variables of C_{mean} as the covariates. The Cox models were weighted to reduce the effects of confounding by baseline characteristics (e.g., BMI and sex) on the C_{mean} effect on 12-week cCDP. Figure 16A-1 shows the relationship between C_{mean} and the expected risk of 12-week cCDP vs control (IFN/Placebo), as predicted by the fitted Cox models. The models indicate that the minimum C_{mean} value that all patients would need to reach in order to achieve a risk reduction of ≥56% versus IFN for patients with RMS and ≥46% versus placebo for patients with PPMS is 21.75 μg/mL and 23.05 μg/mL, respectively. Based on these results and the observed exposure range consideration outlined above, the C_{mean} distribution under higher dose was targeted to lie within 21.75/23.05–83 μg/mL for patients with RMS and PPMS, respectively.

Figure 16A-1: Relationship Between Risk of 12-week cCDP and C_{mean}



The population PK model built on data from the OPERA I/II and ORATORIO studies was used to predict the expected C_{mean} distributions for a higher dose in the OPERAI/II and ORATORIO population. In combination with the fitted Cox models, these distributions were used to estimate the minimum treatment effect as well as the expected percentage of patients with $C_{mean} > 83$ µg/mL for several candidates for higher dose. The results are summarized in Table 16A-1.

Table 16A-1: Summary Statistics of C_{mean} Distribution and Efficacy Properties of Explored Doses

Dose	Pooled OPERA I and II				ORATORIO			
	% with C_{mean} >21.75*	% with C_{mean} >83	1st percentile of C_{mean} distribution	Estimated minimum treatment effects vs. IFN**	% with C_{mean} >23.05 *	% with C_{mean} >83	1st percentile of C_{mean} distribution	Estimated minimum treatment effects vs. placebo**
1200 mg	97.06%	0.26%	19.52	0.62 (0.48 0.79)	94.81%	0.21%	18.32	1.02 (0.80 1.30)
1500 mg	99.74%	1.15%	24.40	0.41 (0.30 0.57)	98.96%	2.07%	22.90	0.55 (0.42 0.72)
1800 mg	100%	4.86%	29.28	Not estimable	99.17%	6.43%	27.48	Not estimable
1200 mg BWT<75 kg & 1500 mg BWT≥75 kg	99.36%	0.26%	23.94	0.41 (0.30 0.57)	98.76%	0.21%	21.32	0.74 (0.58 0.94)
1200 mg BWT<75 kg & 1800 mg BWT≥75 kg	99.62%	0.26%	25.26	0.43 (0.30 0.61)	98.96%	0.42%	23.05	0.54 (0.41 0.71)
16 mg/kg	98.72%	0.13%	20.93	0.48 (0.31 0.55)	96.06%	0.21%	17.88	0.98 (0.77 1.24)
24 mg/kg	100%	1.41%	31.39	Not estimable	99.79%	1.04%	26.82	Not estimable

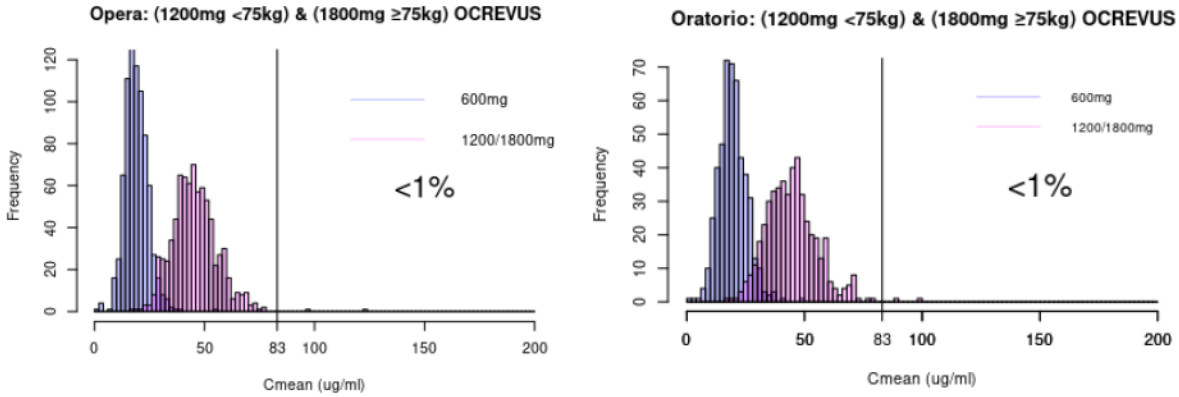
BWT=body weight; C_{mean}=mean concentration; IFN=interferon.

* Efficacy thresholds as defined above were estimated using Figure 16-A1.

** Estimated minimum treatment effects were predicted from the fitted Cox proportional hazards models in Figure 16-A1 by fixing C_{mean} at the 1st percentile of the estimated C_{mean} distributions for candidate doses and calculating the corresponding risk reductions versus control (IFN/placebo).

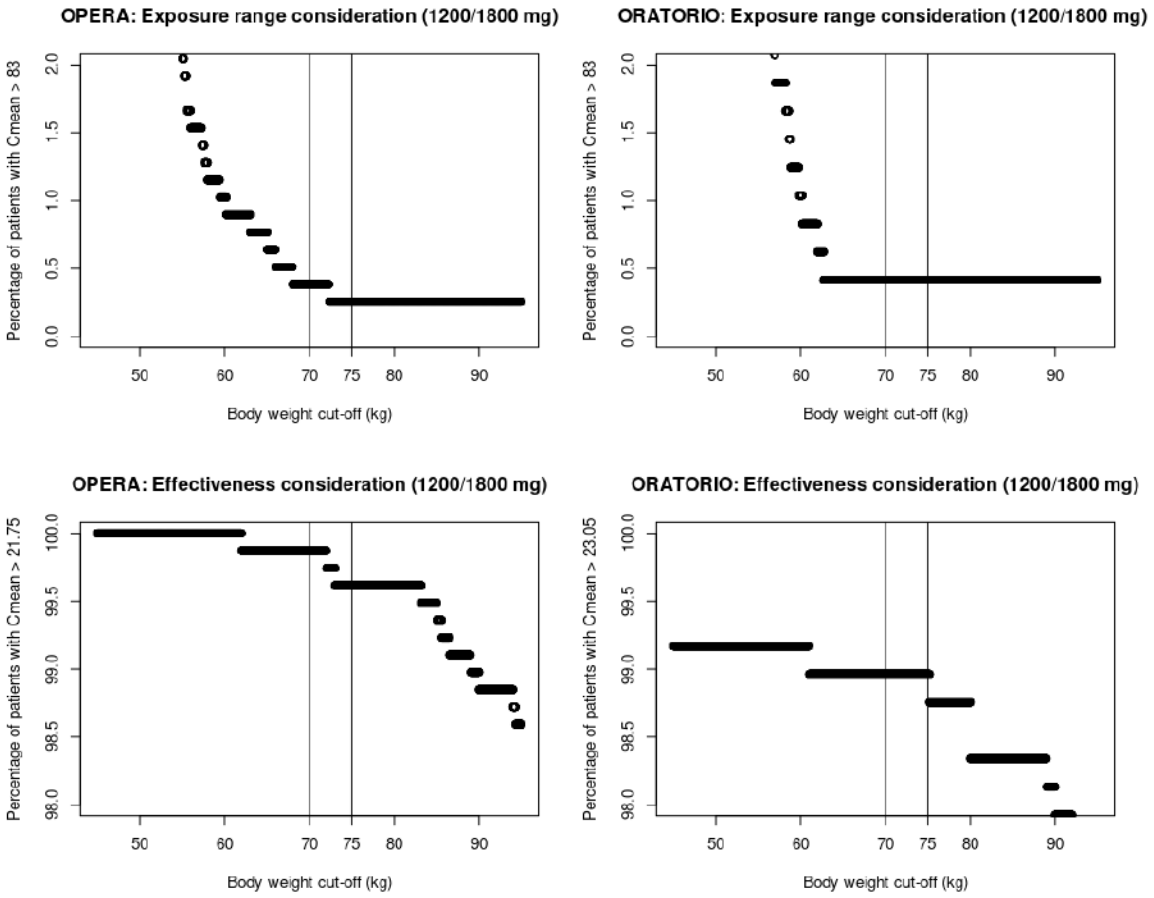
The dose regimen of 1200 mg for patients with body weight <75 kg and 1800 mg for patients with body weight ≥ 75 kg was selected for this study as, for patients with RMS and PPMS, it is predicted to achieve the efficacy consideration and result in $<1\%$ of patients with $C_{mean} > 83$ µg/mL. The expected C_{mean} distributions based on the selected dose regimen is shown in Figure 16A-2. As mentioned, these distributions were estimated from population PK models that were built on data from the OPERA I/II and ORATORIO studies.

Figure 16A-2: C_{mean} Distribution for the Selected Dose Regimen



The body weight cut-off of 75 kg was selected in accordance with efficacy and observed exposure range boundaries for the anticipated C_{mean} distributions. Figure 16A-3 shows that a cut-off of 75 kg is expected to minimize the proportion of patients with $C_{mean} > 83$ µg/mL, and at the same time is able to bring over 98.5% of patients above the efficacy thresholds.

Figure 16A-3: Relationship Between Body Weight Cut-off and the Observed Exposure Range and Effectiveness Considerations



The same analysis described above was also performed for the 24-week CDP outcome. The results suggested that the higher dose regimen of this study will achieve ≥34% risk reduction in 24-week CDP versus 600 mg ocrelizumab for patients with RMS, and ≥27% risk reduction in 24-week CDP versus 600 mg ocrelizumab for patients with PPMS.

Appendix 17
Investigational and Auxiliary Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A17-1 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 RMS 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)

Table A17-2 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 RMS 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 18
Optional CSF Substudy Protocol

PROTOCOL TITLE:	A CSF BIOMARKER SUBSTUDY WITHIN BN42082 TRIAL, PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	BN42082
VERSION NUMBER:	4
TEST PRODUCT:	Ocrelizumab (RO4964913)
REGULATORY AGENCY IDENTIFIERS	EU CT Number: 2023-506467-34-00 EudraCT Number: 2020-000893-69 IND Number: 100,593 NCT Number: NCT04544436
SPONSOR**'S NAME** AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124, 4070 Basel, Switzerland
DATE FINAL:	Refer to the electronic date stamp in the main study.

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OPTIONAL CSF SUBSTUDY PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	A CSF BIOMARKER SUBSTUDY WITHIN BN42082 TRIAL, PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS
PROTOCOL NUMBER:	BN42082
VERSION NUMBER:	4
TEST PRODUCT:	Ocrelizumab (RO4964913)
SPONSOR**'S NAME**:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

OPTIONAL CSF SUBSTUDY PROTOCOL SYNOPSIS

PROTOCOL TITLE:	A CSF BIOMARKER SUBSTUDY WITHIN BN42082 TRIAL, PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS
REGULATORY AGENCY IDENTIFIERS	EU CT Number: 20203-506467-34-00 EudraCT Number: 2020-000893-69 IND Number: 100,593 NCT Number: NCT04544436

STUDY RATIONALE

This substudy will evaluate the effect of a higher dose of ocrelizumab, compared with the approved dose of ocrelizumab, on biomarkers in cerebrospinal fluid (CSF) and blood in patients with relapsing multiple sclerosis (RMS). A positive correlation between serum ocrelizumab exposure quartiles and blood B-cell depletion was observed in the Phase III studies. Moreover, higher exposure quartiles were associated with lower rates of confirmed disability progression (CDP). This substudy will assess CSF biomarkers using measurements of acute inflammation, chronic inflammation, neurodegeneration, and measure ocrelizumab concentration in CSF. This may allow determination of whether a higher dose of ocrelizumab has greater effect on biomarkers relevant to B-cell activity or MS pathophysiology, and their relationship to efficacy.

OBJECTIVES AND ENDPOINTS

This cerebrospinal fluid (CSF) substudy will evaluate the effect on CSF biomarkers of a higher dose of ocrelizumab compared with the approved dose in patients with RMS. Specific objectives and corresponding endpoints for the study are outlined in the following table:

Primary Objective	Corresponding Endpoints
• To compare a higher dose of ocrelizumab versus the approved dose of ocrelizumab	• Change from baseline at Week 48 in the level of neurofilament light chain (NfL) in CSF • Change from baseline at Week 48 in number of CD19+ B-cells in the CSF (cell number/microliter)
Secondary Objective	**Corresponding Endpoints**
• To assess the correlation between changes in CSF biomarkers with those in blood and to compare higher dose of ocrelizumab versus the approved dose of ocrelizumab	• Presence and/or number of oligoclonal bands and/or IgG Index at each scheduled visit • Changes from baseline in levels of B-cell subsets (e.g., naive, memory, plasmablast, etc.) in CSF and blood at each scheduled visit • Changes from baseline in levels of T cells and/or T-cell subsets (e.g., naive, memory, etc.) in CSF and blood at each scheduled visit
Safety Objective	
Safety for the study drug will be explored in the main study. Refer to the main study protocol for BN42082	
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the ocrelizumab concentration in CSF and to investigate the relationship between changes in biomarkers in CSF/blood and ocrelizumab concentration in CSF	• CSF concentration of ocrelizumab
Immunogenicity Objective	
Immunogenicity will be explored as part of the main study. Refer to main study protocol for BN42082.	
Biomarker Objective	**Corresponding Endpoints**
• To identify and/or evaluate 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 AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Levels of B-cells/B-cell subsets, T cells/T-cell subsets, and other cell types (e.g., natural killer cells, monocytes, etc.), functional parameters of B/T/other cell types (activation, cell products), and other biomarkers of inflammation or neurodegeneration/injury in CSF as a reflection of activity in the CNS and compared with blood

OVERALL DESIGN AND STUDY POPULATION

This study is a substudy of BN42082, which is a Phase IIIb, randomized, double-blind, controlled, parallel group, multicenter study to evaluate efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab (1200 mg [patient's body weight < 75 kg at baseline] or 1800 mg [patient's body weight ≥ 75 kg at baseline]) in patients with RMS in comparison to the approved 600 mg dose of ocrelizumab.

Patients in BN42082 will be offered the option to join this substudy. Patients consenting to the optional substudy will follow all main study procedures. In addition, patients will receive two lumbar punctures (LPs) to obtain CSF as part of the substudy: pre-ocrelizumab at baseline and at Week 48 of the double-blind treatment. Patients will be asked to provide an additional optional sample at Week 24, but this is not required to participate in the substudy. Patients who continue treatment with ocrelizumab in the open-label extension (OLE) will be asked for an additional three optional CSF collections at OLE start, and/or after approximately 4 years of follow-up, and/or at treatment discontinuation.

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

Phase:	Phase IIIb	Population Type:	Adult patients
Control Method:	Active comparator	Population Diagnosis or Condition:	RMS
Interventional Model:	Parallel group	Population Age:	18-55 years
Test Product{s}:	Ocrelizumab	Site Distribution:	Multi-site
Active Comparator:	Ocrelizumab	Study Treatment Assignment Method:	Randomization
Number of Arms:	2	Number of Participants to Be Enrolled:	Up to 144 patients from the main study

STUDY TREATMENT

Patients will receive either a higher dose of ocrelizumab (1200 mg [patient's body weight < 75 kg at baseline] or 1800 mg [patient's body weight ≥ 75 kg at baseline]) or the approved 600 mg dose of ocrelizumab

DURATION OF PARTICIPATION

The duration of participation of the substudy is the same as the main study. Please refer to main study protocol for Study BN42082.

COMMITTEES

Please refer to main study protocol for Study BN42082

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
cCDP	composite confirmed disability progression
CDP	confirmed disability progression
CNS	central nervous system
CSF	cerebrospinal fluid
eCRF	electronic Case Report Form
EDSS	Expanded Disability Status Scale
Gd	gadolinium
ICF	Informed Consent Form
IMP	investigational medicinal product
IV	intravenous
LP	lumbar puncture
MRI	magnetic resonance imaging
MS	multiple sclerosis
NfL	neurofilament light chain
NK	natural killer
OCB	oligoclonal bands
OLE	open-label extension
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PK	pharmacokinetic
PPMS	primary progressive multiple sclerosis
PRO	patient-reported outcome
RMS	relapsing multiple sclerosis
SoA	schedule of activities
SPMS	secondary progressive multiple sclerosis
T1Gd+	gadolinium-enhancing T1 lesions
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON BIOMARKERS IN MULTIPLE SCLEROSIS

Although the etiology of multiple sclerosis (MS) remains elusive, it is well accepted that aberrant functioning of both the adaptive and innate immune system, including the dysregulation of B and T cells, occurs in the majority of patients. Despite advances in our understanding of the pathophysiology of disease and recent regulatory approval of a significant number of MS therapies, many patients continue to experience disease progression. Thus, there remains an unmet medical need to develop more effective and well-tolerated therapies for the treatment of MS.

To meet this need, the identification of MS disease biomarkers represents a critical opportunity to potentially understand disease pathogenesis, disease progression, and the mechanism of action of a therapeutic treatment. In the context of MS, biomarkers from the cerebrospinal fluid (CSF) are utilized as a surrogate marker of the pathophysiology occurring within the central nervous system (CNS) tissue (Comabella and Montalban 2014) and brain magnetic resonance imaging (MRI) is utilized as a non-invasive surrogate marker of disease activity (e.g., contrast-enhancing lesions; new and unequivocally enlarging T2-weighted lesions). Biomarkers of neuroinflammation in CSF, such as neurofilament light (NfL) chain, an acute neuronal injury marker, have been correlated with gadolinium (Gd)-enhancing MRI lesions and clinical relapses (Burman et al. 2014, Chitnis et al. 2018) and with response to drug treatment in primary progressive multiple sclerosis (PPMS) and relapsing multiple sclerosis (RMS) (Gunnarsson et al. 2011; Axelsson et al. 2014; Kuhle et al. 2019). Other key sensitive or diagnostic CSF biomarkers of disease include the presence of oligoclonal bands (OCBs), or antibodies produced in the CSF (Link and Huang 2006), as well as the presence of intrathecal memory B-cell plasmablasts (Cepok et al. 2005). These biomarkers suggest a link between CNS-resident B-cell activity and MS pathology.

B-cells are a direct pharmacodynamic (PD) marker for ocrelizumab and have been shown to correlate with exposure levels in the ORCHESTRA Phase III trials (Kletzl et al. 2019). More extensive B-cell depletion was positively correlated with higher exposure of ocrelizumab. The current B-cell test, TBNK, has limited sensitivity and this may preclude its ability to assess very low B-cell counts in blood or CSF. However, more sensitive tests for B-cell numbers, and B-cell subsets other than the TBNK test are available, and will be used here to more finely map the PD response to ocrelizumab in blood and CSF, and how it may relate to efficacy outcomes. In addition, the exposure (pharmacokinetics [PK]) of ocrelizumab in the CSF can be measured and may be related to PD in the CSF and/or efficacy outcomes.

For more background information on MS, see Section 1.1 in Study BN42082.

1.2 BACKGROUND ON OCRELIZUMAB

For information on ocrelizumab, see Section 1.2 in Study BN42082 or refer to the Ocrelizumab Investigator's Brochure and/or local prescribing information for details on the nonclinical and clinical studies of ocrelizumab.

1.3 STUDY RATIONALE

This CSF substudy will evaluate the effect of a higher dose of ocrelizumab, compared with the approved dose of ocrelizumab, on biomarkers in CSF and blood in patients with RMS or PPMS. A positive correlation between serum ocrelizumab exposure quartiles and the blood B-cell depletion level was observed in the Phase III studies OPERA I, OPERA II, and ORATORIO data (data on file). The analysis of confirmed disability progression (CDP) for 12 or 24 weeks stratified by exposure quartiles in the Phase III studies indicated that both RMS and PPMS patients with higher exposure have a reduced risk of CDP. This substudy will assess CSF biomarkers, as a proxy for the CNS compartment, using measurements of acute inflammation, chronic inflammation, and neurodegeneration, and measure ocrelizumab concentration in CSF. This may allow determination of whether a higher dose of ocrelizumab has greater effect on biomarkers relevant to B-cell activity or MS pathophysiology, and their relationship to efficacy.

In the OBOE biomarker outcomes trial (ML29966), it was reported that NfL and B-cells decrease in CSF in patients following treatment with ocrelizumab (Bar-Or et al. 2019). However, while blood B-cell depletion is near complete, CSF B-cells are not fully depleted in all patients. The purpose of this optional substudy is to assess whether a higher dose of ocrelizumab has greater impact on NfL and/or B-cell depletion in the CSF, and to assess other MS biomarkers that may relate to exposure, efficacy, or mechanism of ocrelizumab. Patients consenting to the optional substudy will follow all main study procedures. In addition, patients will receive two lumbar punctures (LP) to obtain CSF as part of the substudy: pre-ocrelizumab at baseline and at Week 48 of the double-blind treatment (DBT). Patients will be asked to provide an additional optional sample at Week 24, but this is not required to participate in the substudy. Patients who continue treatment with ocrelizumab in the open-label extension (OLE) will be asked for an additional three optional CSF collections at OLE start, and/or after approximately 4 years of follow-up, and/or at treatment discontinuation.

2. OBJECTIVES AND ENDPOINTS

This CSF substudy will evaluate the effect on CSF biomarkers of a higher dose of ocrelizumab (1200 mg [patient's body weight $<$ 75 kg at baseline] or 1800 mg [patient's body weight $\geq$ 75 kg at baseline]) intravenous (IV) infusion every 24 weeks in comparison to the approved 600 mg dose of ocrelizumab in patients with RMS.

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

2.1 SUBSTUDY OBJECTIVES

2.1.1 Primary Objective

The primary objective for this substudy is to compare a higher dose of ocrelizumab versus the approved dose of ocrelizumab on the basis of the following endpoints:

- Change from baseline at Week 48 in the level of NfL in CSF
- Change from baseline at Week 48 in number of CD19+ B-cells in the CSF (cell number/microliter)

2.1.2 Secondary Objective

The secondary objectives for this substudy are to assess the correlation between changes in CSF biomarkers with those in blood and to compare higher dose of ocrelizumab versus the approved dose of ocrelizumab on the basis of the following endpoints:

- Presence and/or number of OCBs and/or IgG Index at each scheduled visit
- Changes from baseline in levels of B-cell subsets (e.g., naive, memory, plasmablast, etc.) in CSF and blood at each scheduled visit
- Changes from baseline in levels of T cells and/or T-cell subsets (e.g., naive, memory, etc.) in CSF and blood at each scheduled visit

2.1.3 Exploratory Objective

The exploratory efficacy objectives for this substudy are as follows:

- To assess potential correlation between change in blood or CSF biomarkers of neurodegeneration or inflammation and change in MRI or efficacy outcome measures, including but not limited to reduction in Gd-positive MRI lesions, 12-week cCDP, and Expanded Disability Status Scale (EDSS) score.
- To assess changes in peripheral blood mononuclear cells (PBMCs): B- and T-cell numbers, other cell types, activation markers, functional attributes, activity, and/or molecular status of cells; cellular products to include but not be limited to RNA and protein, and levels of soluble inflammatory markers at each scheduled visit

2.2 SAFETY OBJECTIVE

Safety for the study drug will be explored in the main study. Refer to the main study protocol for BN42082.

2.3 PHARMACOKINETIC OBJECTIVE

The PK objectives for this substudy are to characterize the ocrelizumab concentration in CSF and to investigate the relationship between changes in biomarkers in CSF/blood and ocrelizumab concentration in CSF.

2.4 IMMUNOGENICITY OBJECTIVE

Immunogenicity will be explored as part of the main study.

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this substudy is to identify and/or evaluate 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 AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of but not limited to the following endpoints:

- Levels of B-cells/B-cell subsets, T cells/T-cell subsets, and other cell types (e.g., natural killer [NK] cells, monocytes, etc.), functional parameters of B/T/other cell types (activation, cell products), and other biomarkers of inflammation or neurodegeneration/injury in CSF as a reflection of activity in the CNS and compared with blood

3. STUDY DESIGN

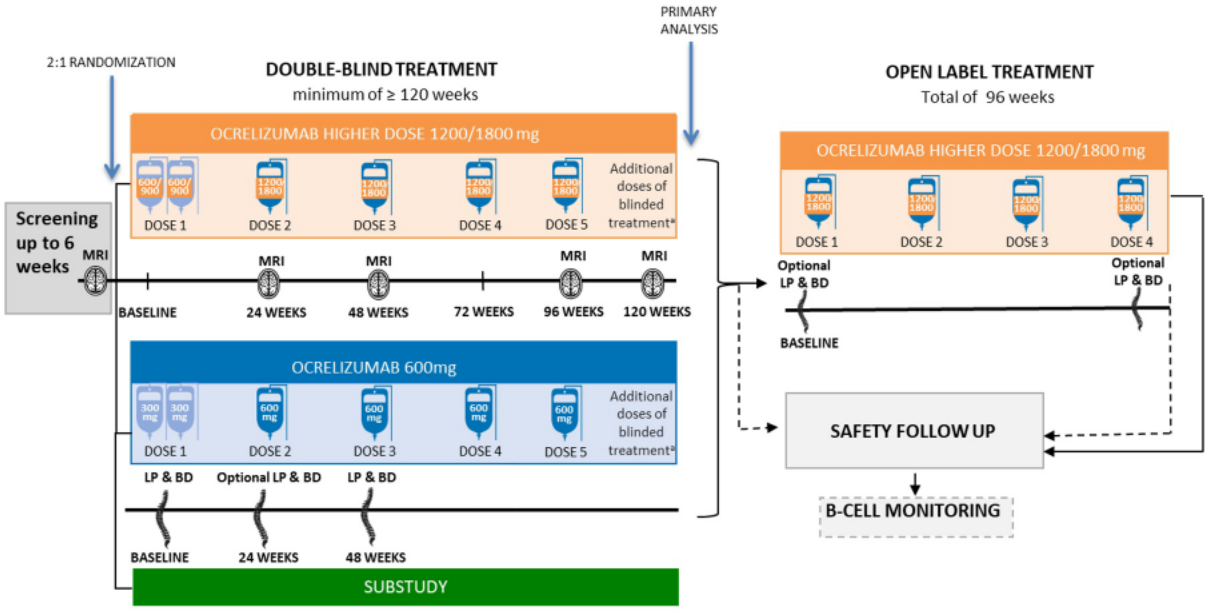
3.1 DESCRIPTION OF THE STUDY

This study is a substudy of BN42082, which is a Phase IIIb, randomized, double-blind, controlled, parallel group, multicenter study to evaluate efficacy, safety, and pharmacokinetics of a higher dose of ocrelizumab (1200 mg [patient's body weight $<$ 75 kg at baseline] or 1800 mg [patient's body weight $\geq$ 75 kg at baseline]) intravenous (IV) infusion every 24 weeks in patients with RMS in comparison to the approved 600 mg dose of ocrelizumab.

Patients in BN42082 will be offered the option to join this substudy. Patients consenting to the optional substudy will follow all main study procedures. In addition, patients will receive two LPs to obtain CSF as part of the substudy: pre-ocrelizumab at baseline and at Week 48 of the DBT. Patients will be asked to provide an additional optional sample at Week 24, but this is not required to participate in the substudy. Patients who continue treatment with ocrelizumab in the OLE will be asked for an additional three optional CSF collections at OLE start, and/or after approximately 4 years of follow-up, and/or at treatment discontinuation.

Figure 3 presents an overview of the substudy design. A schedule of activities (SoA) is provided in the substudy SoA in Appendix A and Appendix B.

Figure 3 Study Design



BD = blood draw; cCDP12 = 12-week composite confirmed disability progression; LP = lumbar puncture; MRI = magnetic resonance imaging.

[a] The double-blind treatment period will continue until the last patient completes at least 120 weeks (a minimum of 5 study drug doses with 24 weeks follow-up after 5th dose, with each dose 24 weeks apart) and the target number of cCDP12 events is reached

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the substudy is the same as the end of the main study. For more information, see Section 3.2 in Study BN42082.

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

Analysis of the data generated as a part of this substudy will not commence until unblinding of the main study.

3.2.1 *Duration of Participation*

The duration of participation of this substudy is the same as the main study. Please see Section 3.2.1 in Study BN42082.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ocrelizumab Dose and Schedule

Please see the main study protocol for BN42082 for the ocrelizumab dose and schedule.

3.3.2 Rationale for Biomarker Assessments

MS is a heterogeneous disease. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond better to ocrelizumab. Potential biomarkers will be assessed to demonstrate evidence of biologic activity of ocrelizumab in patients, compared between the dosing arms. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

B-cells are a direct PD biomarker for ocrelizumab, and a correlation with exposure levels to ocrelizumab was observed in the ORCHESTRA Phase III trial. B-cell subsets have been shown to be predictive of drug response (or loss of response) in rheumatoid arthritis patients, with the return of memory B-cell subsets preceding loss of efficacy in anti-CD20 treated patients (Leandro et al. 2006; Adlowitz et al. 2015). PBMC are also used to assess the levels of B-cell subsets, T cells (which may also respond to ocrelizumab treatment if they express CD20 [Palinchamy et al. 2014]), and to assess B- and T-cell function *in vitro* assays as potential PD, prognostic, or predictive biomarkers.

Biomarkers of neuroinflammation, such as NfL chain, an acute neuronal injury marker, have been correlated with Gd-enhancing MRI lesions and clinical relapses (Burman et al. 2014) and with response to drug treatment in PMS 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 (DiSanto et al. 2017). Other key sensitive CSF biomarkers of disease include B-cell products such as the presence of OCBs, or antibodies produced in the CSF (Link and Huang 2006), as well as the presence of intrathecal memory B-cell plasmablasts (Cepok et al. 2005). Cellular dynamics and the cellular protein of RNA products of cells may allow for an understanding of mechanistic effects of ocrelizumab. These biomarkers suggest a link between B-cell activity and MS pathology, and may act as PD, prognostic, or predictive biomarkers.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to 144 patients with RMS from the main study will be enrolled in this substudy.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for the substudy entry:

- Meet all inclusion criteria to participate in the main study protocol for Study BN42082.
- Signed Informed Consent Form (ICF) for the optional substudy

- Ability to comply with the substudy protocol, including LPs, in the investigator's judgment

4.1.2 Exclusion Criteria

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

- Patients excluded by any exclusion criteria outlined for in the main study protocols for BN42082
- Systemic corticosteroid therapy within 4 weeks prior to baseline (e.g., for recent relapse or chronic use)
    - The screening period may be extended (but cannot exceed 6 weeks) for patients who have used systemic corticosteroids for their MS before screening.
- Previous use of anti-CD20s is allowed if the last infusion was more than 2 years before screening, B-cell count is normal, and the stop of the treatment was not motivated by safety reasons or lack of efficacy
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed in the main study exclusion criteria without appropriate washout as described in the applicable local label

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Refer to the main study protocol for Study BN42082.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN.

Refer to the main study protocol for Study BN42082 for all information relating to formulation, packaging, dosage, administration, treatment discontinuation, compliance, handling, accountability and/or continued access to drug.

4.4 CONCOMITANT THERAPY

Refer to the main study protocol for Study BN42082 for all information relating to prohibited or permitted therapies.

4.5 STUDY ASSESSMENTS

The SoA to be performed during the substudy is provided in Appendix A and Appendix B. All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the substudy must be obtained before performing any substudy-related procedures (including screening evaluations). ICFs 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 screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The screening data for all patients (including those who have been screen failed) will be captured by the sites in the eCRF.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Refer to the main study protocol Study for BN42082 for reporting of all demographic, concomitant medication and medical history data.

4.5.3 Laboratory, Biomarker, and Other Biological Samples

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

Unless the patient gives specific consent for their leftover samples to be stored for optional exploratory research (see Section 4.5. in the main protocol), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum or CSF samples collected for PK analysis may be needed for additional immunogenicity characterization and for PK assay development and validation; therefore, these samples will be destroyed no later than 15 years after the final Clinical Study Report has been completed.
- Serum, PBMC or CSF samples collected for biomarker research and biomarker assay development will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

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.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

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

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

4.5.4 Study Procedure Risk Mitigation

The risk of headache post-LP can be mitigated by expert nurse practitioner or physician collection of the sample, and the use of smaller atraumatic needles (e.g., Sprotte). Atraumatic needles will be provided to sites and personnel with expertise in LP will perform collection in order to minimize such risk.

Spinal epidural or subdural hematoma and brain and spinal hemorrhage are rare but potentially serious complications of an LP. The following precautions are therefore advised:

- Exclude coagulation abnormalities or coagulation results outside the normal range or platelet count below $500x10^9$/L
- Exclude coagulopathies and uncorrected bleeding diathesis
- Discontinue anticoagulant treatments to minimize hemorrhagic risks if medically justifiable
- Patients with dual platelet therapy (ASS and clopidogrel) should discontinue clopidogrel 1 week before the puncture if medically justifiable

Please also refer to the local standard practice recommendations in your country/ at your site, especially if more stringent.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Please see the main study protocol for Study BN42082 for any study treatment discontinuation.

4.6.2 Substudy Discontinuation

Patients may discontinue from the substudy at any time, without affecting their participation in the main studies BN42082. Withdrawal from the substudy does not constitute withdrawal from the main studies.

Patients who discontinue treatment but are still being monitored in the main studies may still participate in the substudy for substudy assessments, even in the absence of treatment, or if taking alternate treatment(s).

If the patient wishes to withdrawal from the substudy and from the main study, please see the main study protocol for Study BN42082 for study treatment discontinuation.

In addition, the Sponsor maintains the right to terminate this substudy 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 substudy.

4.6.3 Substudy Site Closure

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 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

Please see the main study protocol for Study BN42082 for the details on the safety plan.

5.2 SUBSTUDY SAFETY PARAMETERS AND DEFINITIONS

Safety assessments for the substudy will consist of monitoring and recording AEs associated with any substudy procedure. All other assessments of safety should be monitored and recorded as part of the main study protocol for Study BN42082.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and 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). Any adverse event related to a substudy procedure (LP, blood draw) should be reported as part of the BN42082 eCRF

Adverse events should be collected at any visit, including substudy visits.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

Please refer to the main study protocol for Study BN42082 for serious adverse event reporting.

5.2.3 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 problems or issues with your lumbar puncture?"

5.2.4 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.3 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

Refer to the main study protocol for Study BN42082 for the details on the adverse event follow-up. All adverse events, including those specific to substudy procedures, will be followed up in the main studies.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The objectives of this substudy are as follows:

- To compare the changes from baseline in levels of NfL and B-cells between the treatment arms
- To assess the relationship between biomarkers in CSF and blood and their correlation with efficacy outcomes
- To generate the hypotheses about biomarkers of ocrelizumab treatment in patients with RMS

Unless otherwise specified, statistical tests will be two-sided and the statistical significance level will be 5%. Corresponding 95% confidence intervals will be presented as appropriate. No corrections for multiple testing will be applied to the primary, secondary, exploratory endpoint analyses, or interim analysis.

The statistical summaries will be descriptive if not otherwise specified. For continuous variables, the mean, median, standard deviation, 25th and 75th percentiles, minimum and maximum will be calculated. For categorical variables, number and percentage in each category will be displayed.

When establishing statistical significance, parametric and non-parametric methods will be applied as appropriate. Primary endpoints will be analysed using Mixed Model Repeated Measures. Some variables may be appropriately transformed before performing statistical analysis. The Spearman's rank correlation coefficient will be used to evaluate the relationship among the levels of biomarkers and between levels of biomarkers and clinical parameters.

The analysis population will consist of all randomized patients with at least one substudy assessment.

Any additional analyses and 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.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on NfL levels observed in the OBOE study (ML29966) at Week 52 (Bar-Or et al. 2019). Since NfL data are skewed, they will be log-transformed for the purposes of statistical analysis. Assuming a 1.5-fold reduction in NfL levels (pg/mL) between higher dose and approved dose groups, a common SD to be 0.32 (log10 scale), 80% power and 5% alpha, dropout rate of 20% by Week 48, the sample size required for the study is up to 144 RMS patients.

In case less than 144 patients will consent to participate in this substudy or a higher dropout rate is observed, the sample size required to observe a larger than 1.5-fold reduction in NfL levels is: 90 subjects – 2-fold reduction, 27 subjects – 2.5-fold reduction, 15 subjects – 4-fold reduction.

Based on the sample size requirements for changes in NfL levels, effect sizes for changes in number of B-cells which can be detected with 80% power were determined.

With the sample size of 144, 20% dropout at Week 48, and assuming a SD of 0.76 (log10 scale) at Week 24 and 0.97 (log10 scale) at Week 48, it would be possible to detect at least a 2.7- and 3.5-fold reduction in the levels of B-cells (cells/μL) at Week 24 and at Week 48, respectively.

6.2 SAFETY ANALYSES

Safety will be assessed and analyzed as outlined in the main study protocols. AEs for substudy procedures will be summarized descriptively.

6.3 PHARMACOKINETIC ANALYSES

Individual and mean CSF ocrelizumab concentration will be listed and summarized by visit and treatment arm. Graphical summaries may be presented. CSF concentration values collected as part of the substudy will be compared to serum ocrelizumab PK collected in the same patient as part of the main studies.

Additional PK analyses will be conducted as appropriate.

6.4 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Biomarker levels will be presented as absolute values over time and/or changes relative to baseline over time. The relationship between changes in efficacy and safety parameters and levels of biomarker may be examined to assess the predictive properties of biomarkers and their ability to identify patients who might benefit from higher dose of ocrelizumab versus the approved dose. Descriptive or summary statistics will be used to describe biomarker assessments.

6.5 INTERIM ANALYSIS

Refer to the main study protocol for Study BN42082 for the details regarding the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

Refer to the main study protocol for Study BN42082 for the details on data collection and management.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

Refer to Section 8.1 of the main study protocol for Study BN42082 for the details regarding compliance with laws and regulations.

8.2 INFORMED CONSENT

A separate ICF must be signed by the patients to participate in this optional substudy.

Refer to Section 8.2 of the main study protocol for Study BN42082 for the details on the Informed Consent process and requirements.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Refer to Section 8.3 of the main study protocol for Study BN42082 for the details on IRB/ECs.

8.4 CONFIDENTIALITY

Refer to Section 8.4 of the main study protocol for Study BN42082 for the details on confidentiality.

8.5 FINANCIAL DISCLOSURE

Refer to Section 8.5 of the main study protocol for Study BN42082 for the details on financial disclosure.

8.6 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

Refer to the main study protocol for Study BN42082 for the details on study documentation.

8.7 PROTOCOL DEVIATIONS

Refer to the main study protocol for Study BN42082 for the details on protocol deviations.

8.8 MANAGEMENT OF STUDY QUALITY

Refer to the main study protocol for Study BN42082 for the details on the management of study quality.

8.9 SITE INSPECTIONS

Refer to the main study protocol for Study BN42082 for the details on site inspections.

8.10 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.

This substudy will be conducted at the interested sites amongst the approximately 220 sites participating in the main study and will enroll up to 144 patients with RMS. 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 4.5.3.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

8.11 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an investigational medicinal product (IMP) for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a clinical study report and journal manuscript regarding the results of the substudy, as per the Roche publication guidelines. 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.

Refer to Section 9.6 of the main study protocol for Study BN42082 for further details.

8.12 PROTOCOL AMENDMENTS

Refer to the main study protocol for Study BN42082 for the details regarding protocol amendments.

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Appendix A
Schedule of Activities

	Screen	Double-Blind Period														Delayed Dosing Visit	Unsched Visit	Tx Discon Visit
Dose		1			2		3		4		5		6		N[d]			
Visit	1	2 (BL)	3	4	5	6	7	8	9	10	11	12	13	n[d]	N			
Weeks		0	2	12	24	36	48	60	72	84	96	108	120	n	n+12 wks			
Window in days for substudy procedures	As for main study	–7			–7													
Main study visits [a]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Informed consent for the substudy	x																	
Review of eligibility criteria																		
Biomarker serum sample [b]		x			(x)		x											(x) [h]
CSF collection for cellular and fluid biomarker, and PK analysis [c, d]		x			(x)		x											(x) [h]
Whole blood collection for flow cytometry [e]		x			(x)		x											(x) [h]
Blood for PBMC [f]		x	x	x	(x)		x		x		x		x		x		x	x
Adverse event collection [g]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

BL = baseline; CSF = cerebrospinal fluid; Discon = discontinued; MRI = magnetic resonance imaging; N = dosing visit; n= = non-dosing visit; OCB = oligoclonal bands; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Screen = screening; SoA = schedule of activities; Tx = treatment; Unsched = unscheduled; wks = weeks.

[a] Patients in the substudy should follow all main study procedures as outlined in the main study SoA Appendix 1

[b] Blood sample for serum to be collected before ocrelizumab infusion and prior to methylprednisolone (or equivalent) injection at baseline, Week 24 (optional), and Week 48. Blood should be collected on same day of CSF collection to facilitate OCB/IgG Index measurement.

[c] CSF collection to be performed before ocrelizumab infusion and prior to methylprednisolone (or equivalent) injection at baseline, Week 24 (optional), and Week 48. CSF samples to be collected on same day of blood collection to facilitate comparison to OCB/IgG Index and PK measurements (PK will only be measured in post-dose samples).

[d] The collection of the CSF specimen at baseline should ideally not occur within the first 10 days of the brain MRI at screening (and not earlier than 6 days following the brain MRI at screening), to avoid contamination with gadolinium in the biomarker CSF sample. The collection of the CSF specimen should precede the brain MRI at Week 24 and Week 48, to avoid contamination with gadolinium in the biomarker CSF sample. In order to facilitate scheduling before an ocrelizumab dose (e.g., at Week 24 or Week 48), the CSF specimen, followed by the brain MRI, may precede the administration of ocrelizumab by up to 7 business days.

[e] A fresh whole blood sample to be collected on the same day of CSF collection to be processed locally with CSF for flow cytometry analysis. Blood sample should be collected prior to the methylprednisolone injection if at a dosing visit and will be drawn for baseline and indicated post-dose samples.

[f] PBMC cells will be collected from two fresh whole blood samples at indicated timepoints in Schedule of Assessments and sent to the central lab for processing. PBMC samples should be collected prior to the methylprednisolone injection if at a dosing visit and will be drawn for baseline and indicated post-dose samples.

[g] Adverse events resulting from any substudy procedure (e.g., lumbar puncture, blood draw) should be recorded at any visit, as close to the occurrence of the event as possible.

[h] Patients will be asked to give optional treatment discontinuation CSF and matched blood samples, if no other post-dose samples have been collected.

Appendix B
Substudy Open-Label Extension Schedule of Activities

	OLE Screening	OLE								Delayed Dosing Visit	Unschd. Visit	Tx Discon. Visit
Dose		1		2		3		4				
Visit		1	3	4	5	6	7	8	9			
Study week		Wk 0	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	Wk 72	Wk 96			
(Window in days)	–30 to –1	–14	(± 7)	(± 5)	(± 7)	(± 5)	(± 7)	(± 5)	(–14)			
Review of substudy eligibility criteria	x	x										
Main study OLE visits [a]	x	x	x	x	x	x	x	x	x	x	x	x
Informed consent for the substudy OLE	x											
CSF collection for cellular and fluid biomarker analysis [b, c]		(x)							(x)			(x)
CSF sample for PK [b, c]		(x)							(x)			(x)
Biomarker serum sample [d]		(x)							(x)			(x)
Whole blood collection for flow cytometry [e]		(x)							(x)			(x)
Blood for PBMC [f]		(x)							(x)		x	(x)
Adverse event collection [g]		(x)							(x)			(x)

CSF = cerebrospinal fluid; Discon. = discontinued; IgG = immunoglobulin G; MRI = magnetic resonance imaging; OCB = oligoclonal bands; OLE = open-label extension; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Tx = treatment; Unsched. = unscheduled; Wk = week.

[a] Patients in the substudy OLE should follow all main study procedures as outlined in the main study SOA Appendix 2

[b] Optional CSF collection to be collected at OLE Week 0, and/or Week 96, and/or treatment discontinuation, sample should be collected before administration of ocrelizumab and prior to the methylprednisolone injection if at a dosing visit. CSF samples to be collected on same day of blood collection to facilitate comparison to OCB/IgG Index.

[c] The collection of the CSF specimen should precede any brain MRI at OLE Week 0, and/or Week 96, and/or treatment discontinuation, to avoid contamination with gadolinium in the biomarker CSF sample. In order to facilitate scheduling before an ocrelizumab dose (e.g., at OLE Week 0), the CSF specimen, followed by the brain MRI, may precede the administration of ocrelizumab by up to 7 business days.

[d] ONLY collect blood for biomarker serum sample IF the optional CSF sample is collected, blood samples for serum will be collected at OLE Week 0 and/or 96 weeks. Blood should be collected on same day of CSF collection to facilitate OCB/IgG Index measurement. Blood sample should be collected before administration of ocrelizumab and prior to the methylprednisolone injection if at a dosing visit.

[e] ONLY collect blood IF the optional CSF sample is collected, fresh whole blood sample to be collected on same day of CSF collection to be processed locally with CSF for flow cytometry analysis. Blood sample should be collected before administration of ocrelizumab and prior to the methylprednisolone injection if at a dosing visit.

[f] ONLY collect blood IF the optional CSF sample is collected. PBMC cells will be collected on same day of CSF collection from two fresh whole blood samples at OLE Week 0, and/or Week 96, and/or treatment discontinuation, and sent to the central lab for processing. Blood samples should be collected before administration of ocrelizumab and prior to the methylprednisolone injection if at a dosing visit.

[g] Adverse events resulting from any substudy procedure (e.g., lumbar puncture, blood draw) should be recorded at any visit where optional samples are collected, or as close to the occurrence of the event as possible.

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Approval Task	[redacted] 21-Dec-2023 18:33:18 GMT+0000

22 Nov 2024

PROTOCOL CLARIFICATION LETTER

RE: PROTOCOL BN42082: A PHASE IIIB MULTICENTER, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND PHARMACOKINETICS OF A HIGHER DOSE OF OCRELIZUMAB IN ADULTS WITH RELAPSING MULTIPLE SCLEROSIS

Dear Study Investigators and Site Staff,

This letter provides a clarification to Protocol BN42082 (Version 1.0 dated 19 May 2020, Version 2.0 dated 29 March 2021, Version 3.0 dated 27 October 2021, and Version 4.0 dated 21 December 2023), as detailed below.

The revised language clarifies the intent of the protocol and is highlighted in **bold**.

1. Clarification of Open-Label Extension (OLE) phase inclusion criterion

   Protocol Section: 4.1.3 Eligibility Criteria for Open-Label Extension Phase

   Current text: Meet the re-treatment criteria for ocrelizumab (see Section 4.3.2.3)

   Clarification: **Prior to receiving OLE treatment patients need to** meet the re-treatment criteria for ocrelizumab (see Section 4.3.2.3)

   Rationale:
   To avoid excluding patients from entering the OLE due to transiently not meeting the re-treatment criteria during the 30-day OLE screening window (e.g. due to a transient decrease in laboratory criteria) it has been clarified that meeting re-treatment criteria is a requirement for study treatment administration in the OLE phase but not for OLE eligibility.

2. Removal of upper spinal cord MRI acquisition during the OLE phase

   Protocol Section: 4.5.7 MRI Sequences

   Current text: MRI scans of the brain, and also of the upper part of the spine if technically possible will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, and Appendix 3.

   Clarification: MRI scans of the brain, and also of the upper part of the spine if technically possible will be obtained in all patients at study visits as indicated in Appendix 1, Appendix 2, and Appendix 3. **Note, scans of the upper part of the spine will be obtained in the DBT period only.**

   Rationale:
   Upper spinal cord imaging contributes to an exploratory endpoint that will not be extended to the OLE phase. This will therefore lower the assessment burden for patients.

3. Extension of OLE phase visit window to -14/+7 days for non-dosing visits

Protocol Section: Appendix 2 Schedule of Activities: Open-Label Extension

Current text:

	OLE Screening	OLE							
Dose [w]		1		2		3		4	
Visit		1	2	3	4	5	6	7	8
Study week		Wk 0	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	Wk 72	Wk 96
(Window in days)	-30 to -1		(±7)	(±5)	(±7)	(±5)	(±7)	(±5)	(±5)

Clarification:

	OLE Screening	OLE							
Dose [w]		1		2		3		4	
Visit		1	2	3	4	5	6	7	8
Study week		Wk 0	Wk 22	Wk 24	Wk 46	Wk 48	Wk 70	Wk 72	Wk 96
(Window in days)	-30 to -1		**(-14/+7)**	(±5)	**(-14/+7)**	(±5)	**(-14/+7)**	(±5)	(±5)

Rationale:
The main purpose of the non-dosing visit in the OLE phase is to obtain laboratory samples to confirm that the patient meets the re-treatment criteria for the infusion visit taking place approximately 2 weeks later. The window of +/- 7 days is being widened to -14/+7 days to allow additional flexibility with scheduling of the non-dosing visit. Note: the re-treatment laboratory results must be available and reviewed prior to the infusion visit, therefore sufficient turnaround time for central laboratory test results to be reviewed must be allowed.

4. Clarification of contraception requirements

Protocol Section: 4.1.1 Inclusion Criteria

Current text: For females 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 ocrelizumab [Ocrevus] local label) after the final dose of ocrelizumab.

Clarification: For females 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 ocrelizumab [Ocrevus] local label **at the time of initial study consent**) after the final dose of ocrelizumab.

Protocol Section: 4.1.3 Eligibility Criteria for Open-Label Extension Phase

Current text: For females 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 ocrelizumab [Ocrevus] local label) after the final dose of ocrelizumab.

Clarification: For females 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 ocrelizumab [Ocrevus] local label **at the time of initial study consent**) after the final dose of ocrelizumab.

Rationale:
It has been clarified that after the final dose of ocrelizumab in the DBT or the OLE phase, contraceptive methods should be used for 6 or 12 months as applicable by the ocrelizumab [Ocrevus] local label effective at the time of initial study consent. This means that there is no change in this respect for patients and they should follow the contraception requirements after the last dose of ocrelizumab as stated in the current ICF. This is clarified in case of future updates to the contraception requirements for the ocrelizumab standard dose label, as pregnancy data are not available for higher dose ocrelizumab.

5. Use of the paper EDSS form in exceptional circumstances

Protocol Section: 4.5.9.2 Clinician Reported Outcome Assessments and Performance Outcomes

Current text: ClinRO and PerfO instruments will be administered at clinic by a physician or appropriate delegate and completed using an electronic device provided by the Sponsor, at specified timepoints throughout the study (see Appendix 1, Appendix 2, and Appendix 3). Clinicians must complete the official version of each ClinRO and PerfO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol. The data will be transmitted to a centralized database maintained by the electronic device vendor. All instruments apart from EDSS will have a web-based back-up option if required, from study start. EDSS will have a paper back-up option from study start, which is envisaged to be replaced by a web-based option. Please note that once the web-based option is available, the paper option should no longer be used by the study sites.

Clarification: ClinRO and PerfO instruments will be administered at clinic by a physician or appropriate delegate and completed using an electronic device provided by the Sponsor, at specified timepoints throughout the study (see Appendix 1, Appendix 2, and Appendix 3). Clinicians must complete the official version of each ClinRO and PerfO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol. The data will be transmitted to a centralized database maintained by the electronic device vendor. All instruments apart from EDSS will have a web-based back-up option if required, from study start. EDSS will have a paper back-up option from study start, which is envisaged to be replaced by a web-based option. Please note that once the web-based option is available, **all efforts must be made to use the electronic options and the paper option should only be used by the study sites under exceptional circumstances**.

Rationale:
Clarification added that under exceptional circumstances (e.g. when the electronic device and web-based back-up option have first been attempted but are not working/available despite accessing the applicable support systems), the EDSS can be completed using a paper form.

This clarification is to ensure that when paper is used (i.e. under the exceptional circumstances described above), that a standard approach and paper back-up form is used to collect all the required EDSS and administrative information.

6. Clarification that specific pharmacodynamic (PD) and biomarker endpoints are classified as exploratory

Protocol Section: 2.3 PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

Current text: The pharmacodynamic (PD) objective for this study is to characterize the ocrelizumab PD profile on the basis of the following endpoints:

- B-cell levels in blood (including comparing the degree of B-cell depletion between the doses)
- Proportion of patients achieving 5 or less B-cells per microliter of blood
- Proportion of patients achieving 5 or less B-cells per microliter of blood in patients with the high versus low affinity Fc Receptor 3A (FcR3A) genotype per arm

Clarification: The pharmacodynamic (PD) objective for this study is to characterize the ocrelizumab PD profile on the basis of the following endpoints:

- B-cell levels in blood (including comparing the degree of B-cell depletion between the doses)
- Proportion of patients achieving 5 or less B-cells per microliter of blood

The exploratory PD objective for this study is to characterize the ocrelizumab PD profile on the basis of the following endpoint:

- Proportion of patients achieving 5 or less B-cells per microliter of blood in patients with the high versus low affinity Fc Receptor 3A (FcR3A) genotype per arm

Rationale:
Clarification added that certain PD endpoints are considered exploratory.

Protocol Section: 2.5 BIOMARKER OBJECTIVE

Current text: The biomarker objectives for this study are to identify biomarkers that are predictive of response to a higher dose of 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., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety.

Clarification: The **exploratory** biomarker objectives for this study are to identify biomarkers that are predictive of response to a higher dose of 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., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety.

Rationale:
Clarification added that biomarker endpoints described in Section 2.5 are considered exploratory.

Protocol Appendix 18: Optional CSF Substudy Protocol

Analyses described in Appendix 18, the optional CSF substudy are also considered exploratory.

The above clarifications will ensure optimal execution of the study with no direct impact on patient safety or data integrity.

This clarification and changes in the section described above will be incorporated into the protocol in case of a future protocol amendment.

Please ensure a copy of this letter is archived in your Study File and submitted to your Ethics Committee / Institutional Review Board as per local regulations . Should you have any questions, please contact your study monitor.

Thank you for your participation in this clinical trial.

Sincerely,

Signed by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 25-Nov-2024 | 4:22:07 AM CET
[redacted]

[redacted], MD
Medical Monitor